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Summer 2010

Inside the Institute

New Behavioral Medicine Clinic



The Behavioral Medicine Clinic (BMC) is a multidisciplinary evaluation service for children, adolescents, and adults with developmental disabilities including Autism Spectrum Disorders (ASDs) who have behavioral and/or psychiatric challenges.

Through an in-depth assessment process, the BMC interdisciplinary

team - Jim Bodfish, PhD, Associate Director of the Carolina Institute for Developmental Disabilities and Professor of Psychiatry and Pediatrics, and Rob Christian, MD, FAAP, Assistant Professor of Psychiatry and Pediatrics - work together to create a comprehensive intervention plan for patients and families. These plans include a detailed behavioral management plan, recommendations/guidance on implementation of the plan in home, school, or other settings, medical consultation including psychotropic medication recommendations *Continued on page 5*

Early Brain Development in Infants with Fragile X Syndrome

CIDD investigator Dr. Heather Cody Hazlett has been awarded a Research Project Grant (Ro1) from the National Institutes of Health (NIH) to study early brain and behavior development in infants with Fragile X Syndrome (FXS). FXS is one of the leading known causes of mental retardation and occurs in approximately 1 in every 2,000-5,000 live births. The syndrome is a genetically linked disorder caused by a specific mutation of a gene on the X chromosome. The gene, known as FMR1, is responsible for making protein (FMRP) that is important in brain development. The FMR1 mutation causes a diminished production of



Continued on page 6

Newsletter Highlights

Building Alliance: Post Secondary Ed.	2
From the Desk of the Director	3
Postdoctoral Research Training	4
International Meeting for Autism Research	6
Announcements and Your Support	7

At the Carolina Institute for Developmental Disabilities, we support individuals with disabilities and their families by:

- Identifying and applying innovative solutions to complex issues using an interdisciplinary approach
- Studying best practices and translating research into practical applications
- Promoting self-advocacy, leadership, and inclusion by and for individuals with disabilities
- Training world-class leaders and experts in the field of developmental disabilities

A University Center for Excellence in Developmental Disabilities Education, Research, and Service (UCEDD) with core funding from the Administration on Developmental Disabilities (ADD A Developmental Disabilities Research Center (DDRC) with core funding from the Eunice Kennedy Shriver 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)

Building Alliance: Expanding Postsecondary Education Options in North Carolina

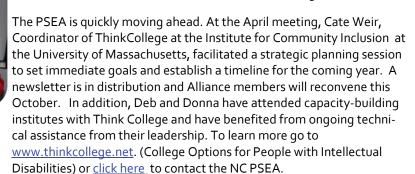
The North Carolina Postsecondary Education Alliance (PSEA) evolved -to address a recommendation from the North Carolina Institute of Medicine (IOM) Task Force to expand options for postsecondary education for individuals with intellectual disabilities. With support from Dr. Bodfish, Deborah Zuver and Donna Carlson Yerby of the CIDD reviewed existing postsecondary education programs nationally and in NC, networked with others in this field, and laid the groundwork for recruiting stakeholders to determine needs in North Carolina.

The Alliance held its initial meeting in October 2009 and subsequent meetings took place in February and April 2010. The diverse group of charter members represents the North Carolina Department of Public Instruction, the North Carolina Council on Developmental Disabilities, higher education, community colleges, NC Department of Vocational Rehabilitation, the NC Legislature, youth advocacy organizations, and family support for individuals with intellectual and developmental disabilities. The PSEA team in-

cludes three interdisciplinary trainees in the LEND (Leadership and Education in Neurodevelopmental Disabilities) program, who participated in the planning and implementation of Alliance activities throughout the year.

Currently, 250 postsecondary education programs for individuals with Intellectual/ Developmental Disabilities exist in 32 states, with data indicating that 58% of individuals who participate in postsecondary education move into paid employment. New provisions in the Higher Education

> Opportunity Act include financial support for students, funding for model demonstration sites, and a national coordinating center.





Donna Carlson Yerby, CIDD Assistant Director of Services Program Development and Evaluation and Learning Specialist, Deb Zuver, Co-director Project STIR

One PSEA goal to create additional models for postsecondary education is already underway.

Kira Fisher, self advocate and coordinator of Youths 4 Advocacy, has been selected to join the cohort of LEND trainees in the upcoming academic year. This Maternal and Child Health program at UNC comprises masters and doctoral students in an interdisciplinary training experience. Kira will gain leadership tools as she enriches the program with her own personal experience as a self-advocate.



Cate Weir, Coordinator of ThinkCollege, Institute for Community Inclusion at the University of Massachusetts

Longitudinal Brain Imaging Study

Results from Joseph Piven, MD's longitudinal brain imaging study of children with Fragile X syndrome have been published online in the Proceedings of the National Academy of Sciences. The study, also involving the CIDD's Heather Hazlett Cody, found that brain changes associated with the most common cause of mental retardation can be seen in magnetic resonance imaging (MRI) scans of children as young as one to three years old. The other senior researcher is Allan L. Reiss, MD, director of the Center for Interdisciplinary Brain Sciences Research (CIBSR) at Stanford University School of Medicine. Click Here to view a full article on UNC Healthcare's website where Dr. Piven was quoted as saying "This means that the brain changes that are indicative of Fragile X syndrome had already taken place before these children were enrolled in our study. In addition, their brains continued to change during the course of the study in ways that we did not expect."

Fumiko Hoeft, John C. Carter, Amy A. Lightbody, Heather Cody Hazlett, Joseph Piven, and Allan L. Reiss (2010). Region-specific alterations in brain development in one- to three-year-old boys with fragile X syndrome. Proceedings of the National Academy of Sciences. 107 (20) 9335-9339.



From the Desk of the Director

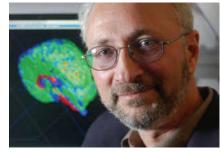
Towards Building a Whole that is Greater than the Sum of its Parts

In May, we had the first of our annual CIDD end-of-year meetings to take stock of where we have been and discuss plans for moving forward. Much has happened since we began this merge of several longstanding units - the CDL, TEACCH, NDRC, FSN -- into a single entity, The Carolina Institute for Developmental Disabilities. Our original vision was to build a comprehensive program at UNC, a program involving the traditional arms of academic medicine of service, education and research, to provide the citizens of North Carolina with the best possible resource for serving the needs of individuals with developmental disabilities. We are clearly well on our way to that goal. However, over the past year we have also learned a few things about building comprehensive programs. We learned that each organization has its own culture and personality and that engineering change is complicated. This past year the TEACCH program moved out of the CIDD. Their new home will be the North Carolina Area Health Education Centers Program (AHEC) within the UNC School of Medicine. AHEC's mission is to provide education and training for the health care work force in NC covering a range of disciplines from medicine (including family medicine, surgery, ob-gyn, mental health), dentistry, pharmacy, nursing to allied health. This past spring I discussed an opportunity with the leadership of the Family Support Network, and a mutual decision was made for them to move into the School of Social Work. Both of these groups will continue to do the excellent work they have been doing for years. As students of development, we all know that developmental processes do not always proceed in a linear, predictable way. Change can be challenging. However, even given these changes, I still believe strongly in the spirit of our original vision – that all of these pieces are part of a whole. Given the complexities of the conditions we treat and research, the complexity of our broad social structure for delivering care, and the need for interdisciplinary perspectives in training; it is clear to me that the way new knowledge is most effectively built, and the way forward, is through close collaboration.

To coin a popular phrase, we are aiming for "a whole that is greater than the sum of its parts". Through the integration of clinical services and clinical observation with both basic and clinical research and interdisciplinary training at all levels, we are aiming to build a comprehensive program that extends from "cells to services". This aim continues to be our primary goal. And, to this end, I believe we are well on our way to achieving it.

In the fall we will open a new 18,000 square foot building for clinical services, clinical research and training. To underscore our joint mission of service, education and research, we will use

that occasion to announce the official merging of the Center for Development and Learning (CDL); and, the Neurodevelopmental Disorders Research Center (NDRC), into a single entity, the Carolina Institute for Developmental Disabilities (CIDD). We will no longer



By Joe Piven, M.D.

be using the names CDL or NDRC. They have served us well but now signal the balkanization of our component parts – which we now need to bring together.

With this new organizational change, there will be some shuffling of our administrative positions. Jim Bodfish, Ph.D. will continue in his leadership role but will join me as Associate Director of the CIDD. Our leadership team will be supported by the CIDD Executive Committee, CIDD External Advisory Board and the CIDD Administrative Core, headed up by Deputy Director, Jeff Low M.B.A. The CIDD will include three primary divisions: "Services", with Director Becky Edmonson, Ph.D., and Assistant Director, Donna Yerby, M.A.; "Education", with Director Steve Hooper, Ph.D. and Assistant Directors: Angela Rosenberg, Ph.D. and Debbie Reinhartsen, Ph.D.; and "Research', with myself as the Interim Director of Research. These efforts are strongly supported by funding from three federal programs: The University Center of Excellence in Developmental Disabilities (or UCEDD), directed by Jim Bodfish; the NC Leadership education in Neurodevelopmental Disorders (or NC-LEND), directed by Steve Hooper; and the NICHD-funded Intellectual and Developmental Disabilities Research Center (or IDDRC), which I will continue to direct. We have the great distinction of being one of only six comprehensive programs in the country housing an IDDRC, LEND and UCEDD program. These three programs epitomize the aims we espouse with the IDDRC generating new knowledge, the LEND disseminating this new knowledge to our trainees; and, application of this new knowledge and training through services as part of our UCEDD program.

With this new organizational chart we are poised to begin plans to functionally integrate the three arms of our Institute – service, education and research. In the coming issues of this newsletter, I will lay out some of the framework for integrating these component parts. I welcome your input and look forward to working together with you to build a leading comprehensive program in developmental disabilities to best serve those with developmental disabilities and their families, in the state of North Carolina.

NIH T₃₂ Postdoctoral Research Training

The research arm of the Carolina Institute provides state-of-the-art training for post doctorates working in the field of developmental disabilities. The mission of the Postdoctoral Research Training Course is to develop 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. The Carolina Institute is thrilled to welcome three new post docs and is honored to continue training three post docs in their second year of the program.

Incoming Post Doctorates:



Jason Yi, Ph.D. completed his Ph.D. in Pharmacology at Duke University in 2009. Over the last year, he has been a 'Research Scholar' in the laboratory of Dr. Michael Ehlers (HHMI), in the Department of Neurobiology at Duke University. Dr. Li has publications in the journals Cell, in press (entitled, "TGF- β Signaling Specifies Axons During Embryonic Brain Development") and Neuron in 2005 (entitled, "Ubiquitin and Protein Turnover in Synapse Function"). He will work with Dr. Klaus Hahn in the School of Pharmacy, to develop advanced molecular probes to investigate, in living neurons, the spatio-temporal dynamics of proteins whose abnormalities are associated with Angelman syndrome. These unprecedented optical sensors are expected to be highly important in the study of IDD-related proteins

and their functions. Dr Yi will specifically test his hypothesis that neuronal activity stimulates Ubea3 (deficient in Angelman Syndrome) in discrete subcellular locations with distinct kinetics to mediate synaptic plasticity. He will design a novel, genetically-encoded biosensor for Ube3a activity and characterize the spatio-temporal dynamics of Ube3a activation in response to neuronal activity and depression.



Jingjun Li, Ph.D. received her Ph.D. in neurobiology and recently completed the Duke Fundamental and Translational Neuroscience Fellowship with Dr. Chay Kuo in the Department of Cell Biology at Duke University. There she studied the role of GABA signaling in postnatal neurogenesis. She has a publication in Neuron (2007) and honors and awards from Beijing Union University. Dr. Li will be working with Dr. Eva Anton to examine how the functionally critical laminar organization and connectivity of neurons in neocortex emerge by examining the primary role of cilia as sensors and conveyors of critical signals in a complex environment. To do this they will use mouse genetic models in

which cilia function can be impaired in a temporal and cell- type specific manner. Arl13b, a small GTPase of the Arf/Arl family, is specifically localized to cilia and controls the microtubule based, ciliary axoneme structure. Mutations in Arl13b result in Joubert syndrome, a neurodevelopmental disorder associated with autistic features in humans. Identification of neurodevelopmental pathways whose disruption is integrally related to the development of brain abnormalities in this condition will inform them about potential therapeutic interventions.



Jason Wolfe, Ph.D. received his Ph.D. in Psychology at the University of Minnesota, working with Dr. Frank Symons, (former faculty at UNC and Frank Porter Graham Child Development Institute) on characterizing the phenomenology of repetitive behaviors underlying self injurious behavior in individuals with intellectual disability. Dr. Wolfe will join the CIDD T32 to work with Dr. Joe Piven and Dr. Jim Bodfish, to study the early development of repetitive behaviors in a longitudinal sample of infants at risk for autism as part of Dr. Piven's NIH ACE Network (IBIS). This work will involve relating these developmental behavioral observations to the maturation of specific neural circuits (measured using diffusion tensor imaging) that may be critical in the development of aberrant repetitive behaviors.

Continuing Post Doctorates:



Sarah Short earned her Ph.D. from the University of Wisconsin, Madison, in Biological Psychology with a specialty minor in Neuroscience. Dr. Short will partner with John Gilmore, M.D. and colleagues during her postdoctoral training at UNC. Dr. Short's research efforts will be aimed at characterizing brain development from the prenatal period through early childhood. Her research projects use structural neuroimaging and diffusion tensor imaging (DTI) in conjunction with cognitive and behavioral measures to understand neurocognitive developmental trajectories in three cohorts of children: typically developing, twins, and high-risk for neuropsychiatric disorders.

Continued on page 5

NIH T₃₂ Postdoctoral Research Training continued



John Anthony Richey, Ph.D., earned a doctorate in clinical psychology from Florida State University in 2009. Dr. Richey's current research involves a three-group comparison (autism, social phobia, control) fMRI study of social processing using a social and nonsocial reward response paradigm. This research is aimed at determining the critical points of overlap in comorbid autism-anxiety versus neurotypical anxiety disorders. Gabriel Dichter, Ph.D. and Jim Bodfish, Ph.D., will serve as co-mentors to Dr. Richey during his post-doctoral training in neurodevelopmental disorders translational research.



Portia McCoy, Ph.D., received her Ph.D. in Neurobiology at The University of Alabama Birmingham in 2008. In her current studies, she aims to characterize the consequences of overexpression of Ube3a, an E3 ubiquitin ligase whose loss causes Angelman Syndrome and overexpression has been implicated in autism, on synaptic function. She will exploit the model system of visual cortical development in the mouse to test the hypothesis that increased Ube3a expression alters synaptic function in neocortex.

New Behavioral Medicine Clinic continued

when applicable, as well as recommendations on possible biomedical drivers of the presenting complaint.

An additional component of the BMC includes training of graduate and medical students involved in the Leadership Education in Neurodevelopmental and Related Disabilities (LEND) program in an interdisciplinary approach to the evaluation and treatment of behavioral challenges in children and adults with developmental disabilities.

An important issue in autism care and research is how to provide sustainable and effective clinical care for the complex real world needs of individuals with ASDs and their families. Individuals with ASDs have clear medical, neurologic, psychiatric, behavioral, psycho-social, and educational needs well beyond those of the typically developing population. The largest burden of illness among this group is in the area of psychiatric and behavioral health needs. Specifically, people with autism experience increased rates of ADHD, anxiety disorders, problematic repetitive behaviors (such as rituals or compulsions), and explosive behaviors. The majority of US families with members who have an ASD report difficulty accessing subspecialty care, most notably mental health care. They also report difficulty with coordinating care and a lack of satisfaction with communication between care providers. There is also little to no research to date on how to best deliver this type of care to individuals and families.



To address these gaps, CIDD is working on an expansion of the BMC program to link with primary care providers around North Carolina. Dr. Christian is leading this effort to develop Community-Academic Partnerships between CIDD, local medical entities, and local behavioral service providers to provide multidisciplinary evaluation, treatment recommendations and care coordination for those with ASDs who also have significant emotional and behavioral challenges. The first proposed partnership, funded by a grant from the NC Translational and Clinical Sciences Institute (NC TraCS), will be between, CIDD, Greensboro TEACCH and Child Health, Inc, an established multidisciplinary pediatric clinic with experience serving children and adolescents with Developmental Disabilities. The partnership is unique in that it combines medical and non-medical experts to evaluate, provide treatment, and coordinate care to best serve this important group of families. This initial Greensboro partnership will hopefully serve as a model for future similar clinical/research partnerships around North Carolina which will ultimately be linked to form a network devoted to delivering a needed clinical service, but also to improving the quality of clinical care delivered to this population via Practice Based Research. As the partnerships and network concept develop, the CIDD sees this endeavor as a platform from which to one day conduct research that will contribute to our understanding of best practices for the ongoing clinical care of individuals with ASDs.

To learn more contact Dr. Rob Christian at rob.christian @cidd.unc.edu or telephone (919) 843-2517.

International Meeting for Autism Research

The 9th Annual International Meeting for Autism Research (IMFAR) was held this past May and attracted over 1,700 participants from around the world. UNC and CIDD presentations at this years meeting are listed below:

- Boyd, B. A., Watson, L. R., Lenhardt, T. W., Dykstra, J., Berry, K. C., Baranek, G. T., Crais, E. R., & Odom, S. (2010, May). Advancing social-communication and play in preschoolers with autism: Initial findings from a classroom-based intervention. International Meeting for Autism Research, Philadelphia, PA.
- Elison, J.T., Chappell, J.C., Sabatino, A., & Piven, J. Microstructure of Looking Behavior in High and Low-Risk Infants: Visual Scanning of Static Faces. Poster (published abstract) at the International Meeting for Autism Research (IMFAR), Chicago, IL. May 2009.
- Dichter, G.S.; Sabatino, A.; Sasson, N; Bodfish, J.W. (2010, May);
 Individuals with Autism Demonstrate Circumscribed Attention During Passing Viewing of Competing Social and Non-Social Stimuli. International Meeting for Autism Research, Philadelphia, PA.
- Gibson, J.N., Sabatino, A., Sabatos-Devito, M., Elison, J.T., Reznick, J.S., Piven, J., & the IBIS Network. Play Behaviors in Infants at High-Risk for Developing Autism. Poster (published abstract) at the International Meeting for Autism Research (IMFAR), Philadelphia, PA. May 2010.
- Greeter, S., Sikich, L., Alderman, C., Rittenberg, A., Turner-Brown, L, Holtzclaw, T., Bodfish, J.W., Richey, J., Dichter, G.S. (2010, May); fMRI of Citalopram Treatment in Autism. International Meeting for Autism Research, Philadelphia, PA.
- Hazlett, H.C., Gu, H., Botteron, K.N., Paterson, S., McKinstrey, R.C.,

- Styner, M., & Piven, J., for the IBIS Network. An examination of brain size in infants at high risk for autism: Preliminary findings from the IBIS. Presented at the International Meeting for Autism Research (IMFAR), Philadelphia, PA. May 2010.
- Lanter, E., Watson, L. R., Freeman, D., Millar, D., Lorenzi, A. P., & Morgan, A. (2010, May). Achievements and correlations among emergent literacy skills in children with autism spectrum disorders. International Meeting for Autism Research, Philadelphia, PA.
- Sabatini, A, Rittenberg, A., Sasson, N. Bodfish, J.W., Dichter, G.S. (2010, May); Cognitive Control of Social and Non-Social Information in Autism: An fMRI Investigation. International Meeting for Autism Research, Philadelphia, PA.
- Watson, L. R., Baranek, G. T., Brown, L. T., Crais, E. R., Reznick, J. S., Wakeford, L., Boyd, L., & Tashjian, C. (2010, May). Parent-mediated intervention for infants at-risk for autism spectrum disorders. International Meeting for Autism Research, Philadelphia, PA.
- Wilson, K. P., Dykstra, J. R., Watson, L. R., Baranek, G. T., & Crais, E. R. (2010, May). Early gesture use in infants with ASD with and without parent-reported regression. International Meeting for Autism Research, Philadelphia, PA.

Early Brain Development in Infants continued

this protein, which in turn results in aberrant brain development and function.

FXS may also be a specific genetic risk factor for autism spectrum disorder (ASD). By studying neurodevelopment in a single gene disorder like FXS, with known brain and behavior abnormalities, researchers can explore neurodevelopmental pathways that may also underlie autism spectrum disorders. Thus, in addition to direct benefit to persons with FXS, the study provides an important model for understanding underlying brain mechanisms and brain—behavior relationships in ASD, and the individual components that comprise these conditions (e.g. social deficits, stereotyped-repetitive behaviors, and language abnormalities).



Heather Hazlett Cody, PhD

Using Magnetic Resonance Imaging (MRI) and Diffusion Tensor Imaging (DTI) to compare the maturity of infants across three time points, at 6, 12, and 24 months of age, Dr. Hazlett and her research team are examining how the trajectory and growth of brain development in infants with FXS compares to early brain development in infants (at high risk for autism) who may later develop an autism spectrum disorder and in infants with typical brain development.

Although knowledge of cognition, behavior and the brain in older children and adults with FXS has grown considerably over the past two decades, data on infants are limited. This is the first longitudinal study examining early brain development in FXS and specifically focused on the role of emerging ASD in FXS. The CIDD is a member of the Autism Centers of Excellence (ACE) Network and is collaborating with two other ACE network sites, Washington University and Montreal Neurological Institute, on the study.

UNC Fragile X Research Registry is currently seeking to enroll families for this study. This is a national recruitment effort. To learn more contact Registry Coordinator, Renee Clark Research Registry@unc.edu; telephone toll-free at 866-744-7879; or visit http://www.fpg.unc.edu/~FXSRegistry/

Announcements:

• Keeping Children with ASD Active:

LEND physical therapy trainee, Catherine Alexander, has developed new materials to help parents encourage their children with ASD to stay active. The brochure entitled Let's Get Moving is available on the CDL website. Click here and scroll down to find the Let's Get Moving heading.



New Autism Concept Award:

John A. Allen, Ph.D., a Post-doctoral Research Fellow at the IDDRC will be receiving a \$75K Autism Concept Award from the Dept. of Defense. This Autism Concept Award, which is part of the Autism Research Program funding mechanism through DOD will help fund a col-



laborative project Ben Philpot, Pd.D. to screen for putative therapeutics that modulate Ube3a expression. Congratulations to John on his first grant as the Principal Investigator.

National Core Indicators Program presents at the AUCD Conference:

Becky Edmondson Pretzel and Debbie Reinhartsen in collaboration with NC Division of MH/DD/SAS, conduct the Consumer Survey of National Core Indicators to gather specific information on healthrelated behaviors and access to care for persons with DD. As the North Carolina



UCEDD, the CIDD's partnerships with other state agencies helped to facilitate the formation of a unique statewide Surveillance Workgroup dedicated to increasing awareness and identifying population concerns and health disparities. The program was well received during a poster presentation at the national AUCD conference.

• CBS News features CIDD IBIS Study:

<u>Click here</u> to view a video that aired on CBS news on April 17th entitled Autism Challenges American Science to Seek Cure. The segment features an interview with CIDD director Joseph Piven, M.D. and a look at the Infant Brain Imaging Study which hopes to provide important clues relevant to early detection of autism and discovering the early changes in the brain for young children with autism.

Send us your comments:

We would love to hear from you if you have comments about our newsletter, ideas for potential articles, or if you would like to be added to our newsletter list! Drop us a line: info@cidd.unc.edu.

Many thanks to our newsletter article writers and editors:

Donna Yerby, Keath Low, and Julia Tarr

Your Support

For more than 40 years, the programs of the Carolina Institute for Developmental Disabilities have provided innovative, high-quality clinical, research, and training activities supporting individuals with developmental disabilities.

The population of our state and nation is growing, and the disability community is growing as well. Children are being diagnosed with developmental disabilities such as autism at an exponential rate. Often, families dealing with a loved one with a disability can feel overwhelmed and need a place to find real answers. Through innovative research that improves practice and enhances education, we will find solutions.

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!

Philanthropic support is essential to the growth of the Carolina Institute for Developmental Disabilities and its goal of improving the quality of life for people with developmental disabilities across North Carolina and throughout the country.

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:" <u>Click Here.</u>

To make a cash donation, please send your check to: The Carolina Institute for Developmental Disabilities, University of North Carolina at Chapel Hill, Office of Development, CB# 3366, Chapel Hill, NC 27599-3366.

Contact: Julia Tarr at (919) 966-4896 or <u>julia.tarr@cidd.unc.edu</u> to discuss your giving options.