Center Line

Bowles Center for Alcohol Studies
School of Medicine, University of North Carolina at Chapel Hill

Our mission is to conduct, coordinate, and promote basic and clinical research on the causes, prevention, and treatment of alcoholism and alcoholic disease.

Volume 18, Number 2, June 2007

Bowles Center Researcher Honored for Pioneering Research and Outreach Initiatives to Combat Fetal Alcohol Spectrum Disorders

As many as 40,000 infants each year in the United States are born with fetal alcohol spectrum disorders—one or more of an array of birth defects that can be caused by maternal alcohol consumption. Fetal alcohol syndrome, characterized by specific craniofacial abnormalities, growth deficiency, and brain dysfunction, is the most severe of the fetal alcohol spectrum disorders. Other consequences of maternal alcohol consumption include alcohol-related neurodevelopmental disorder (i.e., mental impairment without the characteristic fetal alcohol syndrome-associated craniofacial defects) and alcohol-related birth defects (i.e., skeletal and organ defects other than the characteristic craniofacial defects). Fetal alcohol spectrum disorders are associated with lifelong physical and mental impairment that can be severe. In fact, maternal alcohol consumption is the leading known cause of mental retardation in the United States.

Sulik Lab (Left to Right): Gary Duncan, PhD, Deborah Dehart, Scott Parnell, PhD, Jian Dong, PhD, Kathy Sulik, PhD, Elizabeth Myers, Shao-yu Chen, PhD, Marianne Meeker, PhD

Fetal alcohol spectrum disorders cannot be cured. However, they are wholly preventable with maternal abstinence from alcohol during pregnancy. Combating fetal alcohol spectrum disorders entails both education and research: education about the dangers of fetal alcohol exposure and the importance of maternal abstinence during pregnancy, and research to establish the cellular and molecular basis for alcohol-induced birth defects and to quantify the abnormalities resulting from alcohol exposure at specific times throughout fetal development. Dr. Kathleen Sulik, Professor of Cell and Developmental Biology and Director of the Fetal Toxicology Division of UNC's Bowles Center for Alcohol Studies, spearheads cutting-edge initiatives on both fronts.

On the educational front, Sulik has created and led the implementation of targeted programs to inform the public about the dangers of prenatal exposure to alcohol. Sulik's modular science curriculum, *Better Safe Than Sorry: Preventing a Tragedy,* was featured as part of an educational outreach initiative by the Teratology Society at its 47th annual meeting in June. *Better Safe Than Sorry*—developed several years ago with Dr. Marianne Meeker of the Department of Cell and Molecular Physiology at the University of North Carolina and supported by a grant from the National Institute of Alcohol Abuse and Alcoholism—is designed for middle-school and high-school science teachers to use in teaching pre-teens and teenagers about alcohol and its effects on the developing fetus. The curriculum includes educational videos, transparencies to be used in classroom instruction, fact sheets, suggestions for classroom activities, power-point presentations, and lists of web links and print materials containing information on fetal alcohol syndrome. The curriculum, used at schools across the nation, is available to educators and the public on the National Institute of Alcohol Abuse and Alcoholism web site (www.niaaa.nih.gov).

The National Institutes of Health recently awarded Sulik, in partnership with Dr. Meeker and with Dr. Gary Duncan of Science Learning Resources, Inc., a Small Business Technology Transfer grant to develop a second science-based curriculum. Designed for high-school students, *Fetal Alcohol Spectrum Disorders: An "I" Toward Prevention* will adopt a multimedia approach for demonstrating to young people the dangers of fetal alcohol exposure. Using computers to conduct virtual experiments, students will expose fish embryos to alcohol at various

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Kathleen Sulik, Ph.D.

Affiliations

Professor, Department of Cell and Developmental Biology, UNC-Chapel Hill

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Education and Training

PhD in Anatomy, University of Tennessee Center for Health, Memphis, 1976; BS in Biology, Education and Art, Drake University, Des Moines, IA, 1970.

Recent Publications

Green, ML, Singh, AV, Zhang, Y, Nemeth, KA, **Sulik, KK**, Knudsen, TB. Reprogramming of genetic networks during initiation of the Fetal Alcohol Syndrome. Dev. Dyn. 2007; 236 (2): 613-31.

Parnell, SE, Dehart, DB, Wills, TA, Chen, SY, Hodge, CW, Besheer, J, Waage-Baudet, HG, Charness, ME, **Sulik, KK**. Maternal Oral Intake mouse model for fetal alcohol spectrum disorders: ocular defects as a measure of effect. Alcohol Clin Exp Res. 2006; 30(10): 1791-8.

Niakan, KK, Davis, EC, Clipsham, RC, Jiang, M, Dehart, DB, **Sulik, KK**, McCabe, ER. Novel role for the orphan nuclear receptor Dax1 in embryogenesis, different from steroidogenesis. Mol Genet Metab. 2006; 88(3): 261-71.

Sulik, KK. Genesis of alcohol-induced craniofacial dymorphism. Exp Biol Med (Maywood). 2005; 230(6): 366-75.

Website

www.med.unc.edu/alcohol/sulik

developmental stages and will observe and record the structural consequences of alcohol exposure. For example, when exposed to alcohol during the equivalent of the third week of human gestation, the fish embryos develop motor abnormalities such as dysfunctional swimming as well as structural defects involving the brain and eyes. Figure 1 is an image from the curriculum, illustrating normal (below) and alcohol-affected (above)newly hatched fish. The virtual experiments will be accompanied by an educational video demonstrating how such research findings generalize across species.

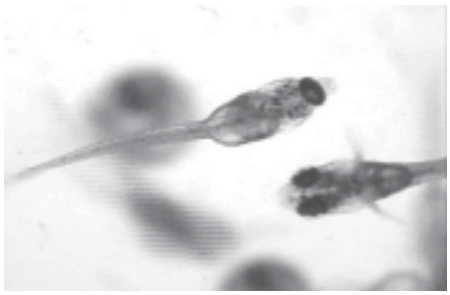

Figure 1: A severely affected newly hatched fish appears to have a single eye as a result of exposure to alcohol at very early stages of its development. The ocular defects are accompanied by abnormalities of the brain.

Sulik's innovation and energy extend beyond her outreach efforts to her research laboratory, where she and her colleagues use state-of-the-art technology to study alcohol's teratogenic effects. Sulik's laboratory is collaborating with Dr. G. Allen Johnson, Director of Duke University's Center for In Vivo Microscopy, to conduct high-resolution magnetic resonance imaging (MRI) of the brains and other target organs of fetal mice. This technology allows the researchers to reconstruct target organs or tissues in three dimensions and to measure precisely their volumes and shapes. One recent series of experiments involved exposing mouse embryos to alcohol via two maternal intraperitoneal injections on the seventh day of gestation (the equivalent of the third week of gestation in humans). This acute exposure to alcohol caused a spectrum of facial and brain abnormalities (Figure 2) as determined on gestational day 17. The most severely affected fetal mice had facial dysmorphology, reduced volume of the brain's cerebrum and olfactory bulbs and enlarged ventricles (i.e., the fluid-filled spaces inside the brain). Less affected mice had less obvious facial dysmorphology and reductions in the volume of specific structures in the front, central area of the brain.

Sulik and her colleagues plan to use MRI technology to develop a comprehensive catalogue of the structural abnormalities associated with alcohol exposure at specific stages of embryonic development. In these experiments, Sulik and her team will assess the consequences of varying the timing of alcohol exposure. For example, they will investigate effects of acute fetal exposure to alcohol on specific gestational days as well as the effects of chronic fetal alcohol exposure via addition of alcohol to the maternal daily diet. Sulik and her colleagues will also determine the effects of varying concentrations of alcohol exposure. "These experiments will help to elucidate the full spectrum of abnormalities associated with fetal alcohol exposure," says Sulik. "We will also be able to address other important questions: What brain structures are always vulnerable to alcohol regardless of the time of exposure? Are there specific facial changes associated with specific brain changes in fetal alcohol spectrum disorders? What timing and amount of fetal alcohol exposure result in effects in the brain but no manifest facial effects? Answers to questions such as these will inform human clinical research and contribute to refining and expanding the diagnostic criteria for prenatal alcohol exposure."

This month, the National Organization on Fetal Alcohol Syndrome (NOFAS) honored Sulik by presenting her with the NOFAS Leadership Award at a Capitol Hill ceremony hosted by United States Senator Linda Murkowski and NOFAS founders the Honorable Tom Daschel and Linda Hall Daschel. NOFAS is an international non-profit organization that is dedicated to prevention of fetal alcohol spectrum disorders and that advocates for and supports individuals who suffer from fetal alcohol spectrum disorders. NOFAS presents its Leadership Award to recognize commitment and leadership in the fight to prevent alcohol-related birth defects. The

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The Director's Column

Fulton T. Crews, Ph.D.
Director,
Bowles Center for Alcohol Studies

This issue of the Center Line highlights two laboratories that are using cutting edge technologies to better understand how alcohol affects the brain. Kathy Sulik's team is leading a research effort to understand the effects of ethanol on fetal brain using imaging technology that could change the diagnosis and treatment of fetal alcohol exposed babies. Studies have found that ethanol can increase fetal cell death, particularly targeting neural crest cells. The effects of ethanol are dependent upon the fetal stage of development, broadening the spectrum of abnormalities and making specific markers difficult. Ethanol-induced effects, including cell death, change the course of brain development in a manner that is not well understood. Further, although ethanol insults the brain at all stages of fetal development, the facial abnormalities associated with fetal alcohol syndrome develop only during first trimester exposure.

The Sulik group is pioneering the use of brain imaging to explore more detailed pathology as well as delayed aspects of brain dysmorphology resulting from earlier exposure. Dr. Sulik is focusing these studies in mice where ethanol consumption, genetics, nutrition and other variables can be controlled. These studies will provide new insights on brain morphology and development. This is particularly exciting since human brain imaging is well ahead of mouse brain imaging. Sulik's controlled experimental dysmorphology will be readily translated to human findings to determine if brain imaging can be used to establish insults in brain and develop targeted therapy.

Similarly, Dr. Donita Robinson is developing new methodologies to understand how the brain directs behavior. We know that dopamine is a key transmitter involved in attention, reward and learning. Using multiple arrays, electrochemical detection and behavioral analysis, she will dissect the underlying changes in brain that drive ethanol-induced behaviors. This is challenging but could provide the basis for investigating drugs that block pathological ethanol-induced behaviors.

This is an exciting time in brain research. Kathy Sulik's efforts to follow brain dysmorphology could lay the foundation for new diagnostic and therapeutic efforts to make children healthy. Donita Robinson may find why people lose control over their behavior when addicted and develop strategies to help them regain control. ■

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award attests to Sulik's tireless commitment to and pioneering leadership in research and education on fetal alcohol spectrum disorders. ■

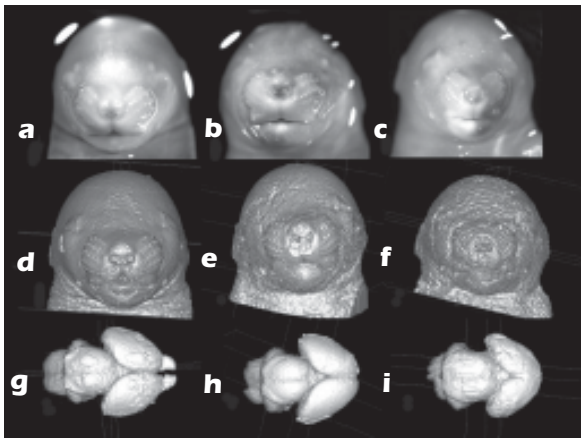


Figure 2: High resolution magnetic resonance imaging of normal and alcohol-damaged mouse fetuses allows detailed study of the brain and face. Light microscopic images (a-c) as well as 3-D MRI reconstructions of the faces (d-f) and brains (g-i) of gestational day 17 mouse fetuses illustrate varying degrees of affect in the abnormal fetuses (center column and that on the reader's right).

Post-Doctoral Fellowships in Molecular and Cellular Studies on Alcohol's Actions

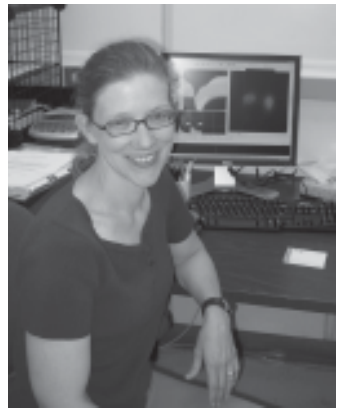
The Bowles Center for Alcohol Studies is offering post-doctoral fellowships in a multidisciplinary training program. Research is focused on molecular and cellular studies on alcohol actions. Applicants must have an M.D. or Ph.D., U.S. citizenship or permanent residency, and an interest in alcohol research.
For more infomation, visit us online .

www.med.unc.edu/alcohol/postdoc

Robinson Lab Moves into Bowles CAS

Donita Robinson, Ph.D., recently acquired new lab space in the Bowles Center for Alcohol Studies. The Robinson Lab will focus on brain mechanisms during alcohol drinking in rats with the aim of understanding the neuronal circuitry that underlies alcohol-motivated behavior.

To study these brain mechanisms, the Robinson Lab makes electrophysiological and electrochemical measurements in the nucleus accumbens, a pivotal component of the brain circuit associated with reward and motivated behavior. For electrophysiological measurements, a voltage follower monitors action potentials of nucleus accumbens neurons that are detected at chronically implanted microelectrode arrays. To measure electrochemical changes, a current follower monitors fluctuations in dopamine concentrations on a subsecond time scale. These measurements are made in real-time while the animal actively seeks and drinks alcohol. Together, these techniques provide an important window on information processing in the nucleus accumbens.



Donita Robinson, Ph.D.

Robinson, assistant professor in the UNC Department of Psychiatry and the Bowles Center for Alcohol Studies, has been a faculty member of the Bowles Center since 2003. In 2000, she received her doctorate in neuroscience at the University of Texas at Austin and joined UNC for her postdoctoral work in analytical chemistry.

Robinson has been studying ethanol's effects on the brain for nearly ten years and recently received a new grant from the Alcoholic Beverage Medical Research Foundation. The grant, entitled *Neurophysiological adaptations in the nucleus accumbens to chronic and repeated ethanol exposure*, will study the changes in nucleus accumbens activity associated with alcohol dependence and withdrawal. The study will also compare different patterns of alcohol exposure and withdrawal and will characterize neuronal firing rates both during the exposure period and the withdrawal phase.

"I believe that the study of nucleus accumbens function is a crucial step in understanding neural adaptations underlying the transition from moderate drinking to alcohol dependence," said Robinson. ■

The Bowles Center for Alcohol Studies

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To become involved in our mission, call Elizabeth Thomas at (919) 966-4977 or email ethomas@med.unc.edu.

For treatment information call UNC Health Care's Alcohol and Substance Abuse Program at (919) 966-6039 or (888) 457-7457.

www.med.unc.edu/alcohol

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