The Director's Column

Fulton T. Crews, Ph.D.
Director,
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Alcohol Studies

The Bowles Center for Alcohol Studies mission is to do basic and clinical research on the causes, prevention and treatment of problems caused by alcohol abuse and alcoholism. The NIAAA Alcohol Research Center grant is a key element in carrying out this mission. The Center grant brings our faculty together better than any other factor. The structured meetings on research findings and methodology promote discovery among multiple laboratories increasing productivity and discovery by all. Collaborations bubble up between experts in behavior and experts in neurobiology and genetics. The Center grant is a catalyst of our science that synergizes innovation, increasing productivity and making discovery more fun.

The Center Grant also is the basis and an important resource for much of our outreach activities. Leadership across communities is essential if the Center is going to use its scholarship to improve prevention, diagnosis, intervention and treatment. These efforts, ranging from youth to health professional students to treatment professionals, open new opportunities. Discoveries in the basic science laboratory need to be translated to clinical studies, which when successful need to be translated to science-based treatment protocols to be followed by the majority of clinicians, not just those at the Medical School. Our research covers a spectrum of alcohol-related biological and environmental risk factors that induce pathological behaviors as well as tolerance, withdrawal and neurobiological changes in addiction. This new knowledge represents unique targets, each of which could be used to reduce risk or treat alcohol addiction. The Center grant provides not only the unifying research themes that are poised to understand the elements of risk for dependence but also provides for educating therapists on these discoveries.

In closing, I would like to congratulate my faculty in the Bowles Center for Alcohol Studies for the success of their collaborative research efforts. We are grateful to our scientific advisory board, Drs. Charness, Diamond, Ehlers, Harris, Hoek and Randall, for their continuous advice, critiques and discussion of our research strategies. We thank the National Institute of Alcohol Abuse and Alcoholism for 15 years of support of our Center grant. It is our hope that we will make major discoveries over the next five years that translate to better health for all. ■

The Bowles Center for Alcohol Studies

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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.

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CAS Awarded Five-Year, Multimillion-Dollar Center Grant: Molecular and Cellular Pathogenesis in Alcoholism

A holiday surprise arrived early last December for researchers at the University of North Carolina's Bowles Center for Alcohol Studies. The Center received official word from the National Institute of Alcohol Abuse and Alcoholism (NIAAA) that its Center grant renewal application – that will provide $10 million dollars of research support over 5 years—was to be funded. Only a handful of Alcohol Center grants are awarded, and competition for these prestigious and lucrative awards is fierce. The December 2007 renewal is the Bowles Center's second renewal and its third consecutive five-year award; an exceptional run of success for alcohol research centers. This renewal was the culmination of a 14-month process during which laboratories contributing to the Center grant application evaluated their progress, generated and refined new hypotheses, and identified areas of synergy. The investigators will apply multidisciplinary approaches to elucidate the causes, consequences and potential treatments for alcohol abuse and alcoholism.

"Thorough preparation was crucial," says Dr. Fulton Crews, Director of the Bowles Center for Alcohol Studies and Program Director for the Center Grant. "We began our work for this renewal in October 2005 with a retreat at which all of the Bowles Center laboratories and several external advisors met to review current research initiatives and generate ideas for new projects. Based on discussions at the retreat, we formed several research teams that met monthly to discuss progress and new ideas. Our goal was to identify unifying hypotheses and common areas of study where we expected our collaborative efforts to yield more progress than could be gained from individual laboratories working in isolation."

For Center Grants, the integrated and synergistic aspects of the research are key. Center Grants differ from grants awarded to individual laboratories in their requirement for coordinated research initiatives involving several laboratories. Center Grants are built on the premise that discoveries are facilitated by cooperation among laboratories, each contributing its particular scientific expertise and technological strengths. As Center researchers worked to prepare the grant renewal application, they came to realize that much of the potential for research integration and synergy lay in their collective ability to investigate the full spectrum of the progressive pathology of alcoholism.

The progressive pathology of alcoholism is defined behaviorally by increases in both the amount of alcohol consumed and the frequency of bouts of alcohol drinking. The path to alcoholism begins with initial experimentation with alcohol, followed by increasing alcohol consumption, and the development of alcohol dependence with behavioral and

Continued on next page

Center Grant Faculty (left to right): Shao-yu Chen, Ph.D., Jian Zou, M.D., Ph.D., A. Leslie Morrow, Ph.D., David Overstreet, Ph.D., Michael Chua, Ph.D., Liya Qin, Ph.D., Kirk Wilhelmsen, M.D., Ph.D., Clyde Hodge, Ph.D., Joyce Besheer, Ph.D., Darin Knapp, Ph.D., George Breese, Ph.D., Robert Gwyther, M.D., Kathy Sulik, Ph.D., Fulton Crews, Ph.D. and Donita Robinson, Ph.D.

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physiological manifestations of addiction. With time and sufficient doses, alcohol consumption is associated with chronic inflammation and damage to the brain and other organs. Bowles Center researchers are particularly interested in the cellular and molecular mechanisms that underlie the stages in this progression. The various laboratories in the Bowles Center use animal models that address different phases of pathology on the road to development of alcoholism and alcohol-induced tissue damage. In fact, the research of the collective laboratories encompasses the full spectrum of alcoholic progression from experimentation through dependence and drinking-induced tissue damage.

A scientific core of the Center Grant links all research components through support for studies of gene expression, cellular biology and sophisticated microscopy. The core sponsors informal science meetings that stimulate hypothesis among faculty, post-doctoral fellows and graduate students. The research ranges from the human genetics of alcohol response, a known factor regulating risk for alcohol dependence, to alcohol-induced brain cell damage in adults and fetuses that occur with the high alcohol consumption or alcohol dependence.

Dr. Kirk Wilhelmsen investigates genetic determinants of human alcohol sensitivity and relates them to variants in CYP2E1, an enzyme that is induced by alcohol in brain and other tissues, metabolizes alcohol and increases oxidative stress.

Drs. Clyde Hodge and Joyce Besheer model alcohol drinking and motivation to drink in mice that voluntarily drink alcohol, progressively increase drinking, and show relapse heavy drinking after abstinence. Molecular signals in specific brain regions, particularly a kinase called ERK, change in association with motivation to drink, and drugs that block these signals can block relapse drinking.

Dr. Donita Robinson studies motivation to drink using multi-electrode arrays that follow the firing patterns of neurons with special electrochemical detectors for dopamine that measure synaptic release while rats respond to a light cue letting them known they can press a lever and get alcohol. This approach allows an investigation of the brain circuitry that drives motivation to drink and compulsive uncontrolled drinking.

Drs. George Breese, Darin Knapp, David Overstreet and Todd Thiele follow persistent changes in anxiety-like behaviors that occur with repeated drinking and abstinence cycles. Brain region specific changes in various signaling proteins, including inflammatory cytokines, lead to a progressively increasing withdrawal anxiety that can be blocked with selective drugs providing mechanistic insights as well as potential new therapies.

Drs. Leslie Morrow and Sandeep Kumar investigate the mechanisms of alcohol dependence-induced changes in inhibitory transmission mediated by GABA-A receptors including the role of specific subtypes of protein kinase C. These studies relate alcohol dependence to alterations in phosphorylation and cell surface expression of GABA-A receptor subtypes that determine how brain cells respond to alcohol, GABA and other endogenous modulators.

Drs. Fulton Crews, Liya Qin, and Jian Zou identify mechanisms of neuroinflammation and brain damage that result from exposure to binge drinking of alcohol. Studies investigate how cytokines, oxidative gene induction and other processes alter brain structure and function in brain regions that contribute to self-control, impulse inhibition and goal setting, brain areas important in protecting against dependence.

Similarly, Drs. Kathy Sulik and Shao-Yu Chen work on brain damage in the fetal brain following high alcohol exposure. Innovative methods in brain imaging coupled with molecular studies of oxidative cell damage are hoped to allow better understanding of the molecular mechanisms and the course of fetal pathology. These studies could lead to new forms of diagnosis and specialized therapy for fetal alcohol-exposed babies.

Together the Center has overlapping themes of alcohol-induced changes in genes, signaling and pathology that range from the behavioral pathology of initial drinking, to tolerance and physical dependence, to marked brain damage that occurs with binge and alcoholic drinking. The mechanisms that underlie this spectrum of pathology overlap substantially and this overlap stimulates discovery among all the research components.

The Center Grant includes an educational core that complements the scientific core. The educational core includes several initiatives targeting health professionals (including clinicians, counselors, and policymakers) and legal professionals with information on alcohol abuse and its prevention and treatment (see article, page 3).

Reflecting on the wide-ranging research and educational activities made possible by the Center Grant, Crews likens the potential for advancing prevention and treatment of alcoholism to progress in the prevention and treatment of tobacco dependence. In the past two decades, tobacco research has elucidated the harmful effects of tobacco and led to new therapeutic approaches for nicotine dependence. This research has led to improvements in public health and significant changes in public policy. "The Center Grant positions us to begin to do the same for alcohol dependence," says Crews. "Our research reveals how alcohol changes the brain and how alcohol dependence develops over time. By educating the public, particularly young people, about these effects, we arm them with information that can prevent them from becoming alcoholics."

"By defining therapeutic targets for alcohol dependence, we can hope to treat alcoholism in those who have become addicted to alcohol. Although alcohol is different from tobacco and can be beneficial in moderation, alcohol also has more immediate negative consequences than the delayed illnesses (cancer and heart disease) related to tobacco use. We look forward to successful education-prevention, intervention and treatment coming out of our research efforts." ■

Bowles CAS Reaches Out to NC and the World

Bowles Center for Alcohol Studies (CAS) faculty members are working on several projects that will improve awareness, prevention and treatment of alcoholism and alcohol-related disorders. These projects target a whole spectrum of learners, from health professionals to children across the state of North Carolina and the World. These projects are supported in part by our newly funded NIAAA Center grant.

Each year, the Center co-hosts the annual Carolinas Conference on Addiction and Recovery, an educational offering that translates cutting-edge research to practice. Through a partnership with the Addiction Recovery Institute, this has become a major statewide conference. Its goal is to disseminate the latest alcohol research and treatment methods to state health professionals and professionals-in-training. The conference brings together different groups of treatment professionals providing an opportunity to exchange thoughts and ideas that range from recommendations in public policy and state support of substance abuse treatment to genetics and brain dysfunction that contribute to dependence. The conference also includes judges and others within the NC criminal justice system, as well as stakeholders in the substance abuse treatment community. It provides a forum to connect physicians, social workers, substance abuse counselors, psychologists, scientists and others that allow the Center to contribute leadership in an effort to reduce alcohol problems across North Carolina and beyond.

A new program focused on students and public service is the Bowles Fellows Program. Health professions students, including those in medicine, dentistry, pharmacy, nursing, public health and social work are targeted. Each year, the CAS will fund students who have a free summer or other volunteer time, to design and implement an outreach program that focuses on an unmet alcohol-related need. The service projects focus on at-risk communities and will help develop student leadership. An initial fellowship involved medical students spending time at clinics with education-prevention materials on fetal alcohol effects available in both English and Spanish. "This program is designed to foster lifelong commitment to public service," said Kathy Sulik, Ph.D., professor of cell and developmental biology.

CAS faculty members, in conjunction with the Office of Educational Development (OED) at UNC, continue to work to strengthen alcohol and substance abuse education in the medical school curricula. Across the Center, faculty teach aspects of the medical curriculum with the knowledge that primary care physicians can provide a major impact through screening, interventions and referrals that could change the face of addiction and abuse. "The diseases caused by alcohol and drug abuse present the largest potential for preventing human suffering and reducing costs to the society as well as to the individual," said Robert Gwyther, Ph.D., director of pre-doctoral education. "The UNC School of Medicine offers every medical student a curriculum in the study of addiction diseases and their potential treatments."

An outreach initiative with great success and future promise is the development of prevention and education curricula for middle and high school students. A middle school experiment-curriculum kit, "Better Safe than Sorry," distributed over 2,000 free kits through Carolina Biological Supply Company. Each kit provides a teacher with written and video materials, fact and work sheets, transparencies, a learning game and supplies for a simple hands-on science experiment. The "Better Safe than Sorry" middle school curriculum continues to be distributed around the world. Dr. Crews estimates that 2000 kits will allow teachers to educate approximately one million students over five years. If these children share what they learned in class with their family, the impact may be even greater. Dr. Kathy Sulik and other CAS faculty are developing a new and improved prevention-education curriculum directed at high school science and health students. The curriculum will include virtual studies on fish and human development, including exposure of fish embryos to alcohol that shows alcohol's adverse impact on embryogenesis.

In addition, working with the UNC Morehead Science Center, which serves more than 100,000 grade school students each year, the CAS is developing three educational modules on alcohol use and abuse. The Science Center employs a team of instructional designers, educators and multimedia specialists that create educational experiences for school groups. The modules will focus on fetal alcohol spectrum disorders, the juvenile brain and alcohol, and alcohol and behavior. The objective of this outreach initiative is to stimulate interest in science and clinical research, as well as inform young students of the morbidity and effects of alcohol use and abuse.

Initially, Morehead will develop fetal alcohol curricula with Dr. Sulik and other faculty involved in developing virtual and real experiments on fish embryos and alcohol's disruptive effects on development. A second curricula will follow brain development from birth to old age, including how brain development relates to the development of abilities in music, athletic movement and personality. How alcohol can impact the brain and life course will be interwoven within the developmental theme. The final theme will involve behavior and the brain, including experiments on how motivation, anxiety and mood are studied and are changed by environment-genetic interactions. The Center hopes these efforts will impact broad groups of youth across North Carolina increasing interest in science and healthy behaviors.

The CAS has a web site that is often visited and contains information on the Center as well as a broad variety of information on alcohol and its impact on social and medical problems. It is http://www.med.unc.edu/alcohol. ■