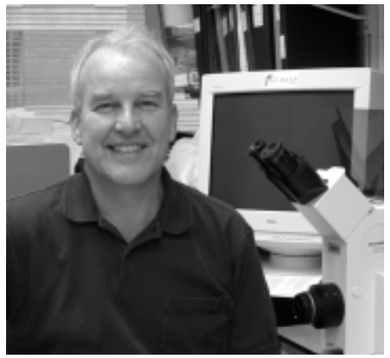
Novel Gene Delivery Attenuates Seizures and Neuronal Death

Bowles Center for Alcohol Studies researcher, Thomas A. McCown, Ph.D., recently published a paper in Nature Medicine entitled "Attenuation of seizures and neuronal death by adeno-associated virus vector galanin expression and secretion" (*Nature Medicine* (2003) 9:1076-80).



Thomas J. McCown, Ph.D.

This work marks an important breakthrough for all disorders that may involve neurodegeneration and seizures – and alcoholism meets this criterion. When speaking on his work, Dr. McCown says, "The means by which we accomplished our goals also provides a unique experimental tool that can be used to investigate brain mechanisms that contribute to alcohol abuse."

For example, recent studies have established an association between a specific brain peptide, neuropeptide Y, and alcohol consumption. Using the technology he and his collaborators have developed, it is now possible to produce this neuropeptide in specific brain areas for extended periods of time and directly determine if neuropeptide Y influences alcohol consumption. Dr. McCown adds, "In fact, these exact studies are just beginning in collaboration with another Bowles Center Member, Dr. Todd Thiele. Such knowledge will lay the foundation for improved, novel treatment approaches."

New treatment approaches are needed to deter the many alcohol withdrawal symptoms that individuals face. During withdrawal, most individuals experience tremors, seizures, hallucinations, and alcohol craving. This makes the completion of the withdrawal much harder for most and they either return to alcohol abuse to stop the withdrawal symptoms or turn to pharmaceutical methods for treatment that will ease or eradicate the withdrawal symptoms. For years, scientists have tried to find better methods for treating patients who are desperately trying to recover from alcohol abuse. Dr. McCown's work is bringing us closer to achieving those goals and making the lives of many people better across the globe.

The Bowles Center for Alcohol Studies

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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

Welcome, Angela Paige!

We would like to welcome Angela Paige, our new Assistant Director of Development. Mrs. Paige will work to gain support to advance the research, treatment, education, and prevention efforts of our Center. She is a UNC Communications Studies graduate with experience in psychology. Mrs. Paige says "I am open to speak with anyone who would like to learn more about our Center." For more information about how you can support our efforts, contact Angela at (919) 843-6204 or angela_paige@med.unc.edu

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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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Pharmacotherapy for Alcoholism: Coming of Age

Pharmacotherapy for alcoholism is coming of age, according to Dr. James C. Garbutt of the University of North Carolina's Bowles Center for Alcohol Studies, the Alcohol and Substance Abuse Program, and the Department of Psychiatry. "We have been successful in developing medicines for complex brain disorders such as depression, anxiety, schizophrenia, and bipolar disorder, but until recently we've lagged behind with alcoholism," says Garbutt. "That is changing. We now have several potential new therapies under investigation and are developing ways of improving existing pharmacotherapies. It is an exciting time to be an alcohol researcher."

Alcohol and Substance Abuse Program: Front, L to R - Peggy Whiting, Arleta Brooks, J.C. Garbutt (Medical Director), Kathy Grace; Rear, L to R: Bill Renn (Director), Alexei Kampov-Polevoi, Tim Sannes, Ben Lancaster, Not Pictured: Meghan Cody

Garbutt attributes this coming of age of pharmacotherapy for alcohol dependence to a confluence of developments. With advances in basic-science research, knowledge of the brain mechanisms underpinning addiction and alcohol dependence has increased tremendously over the past decade; and new pharmacologic targets for intervention have been identified. As understanding of the neural basis of alcoholism has grown, the pharmaceutical industry has become more active in exploring pharmacologic targets for alcoholism and has supported large clinical studies of potential treatments. These studies, in addition to providing data on the effectiveness of treatment, have yielded information about patient-specific factors that influence response to therapy. This information helps to tailor new and existing therapies to particular needs. These studies have also led to improved research methodologies by helping investigators to refine ideas about how best to measure the impact of therapy.

Vivitrex®, a long-acting injectable formulation of naltrexone, is a product of some of these developments. Naltrexone was initially introduced for alcohol dependence in the United States in 1994 as an oral tablet taken daily. Results of several clinical trials considered in aggregate suggest that naltrexone added to substance abuse treatment or counseling reduces heavy drinking among patients who take the drug as prescribed. Although several studies show that oral naltrexone could enhance the probability of an alcoholic's being completely abstinent, this effect was less pronounced than the reduction in relapse to heavy drinking.

While the body of evidence suggests efficacy of oral naltrexone, it was not significantly better than placebo (i.e., an inactive sugar pill) in all studies. One of the main factors influencing the effectiveness of naltrexone is patients' compliance with therapy—that is, the degree to which the drug is taken as prescribed. In several clinical trials, and as seen in clinical practice, patients who did not take naltrexone as prescribed did not benefit whereas those who took at least 70% to 90% of prescribed medication were more likely to experience reductions in the amount and/or frequency of drinking. Many patients prescribed oral naltrexone do not take all of their medication because they experience side effects (particularly fatigue and nausea), are ambivalent about quitting drinking, or do not remember to take their medicine every day.

Long-acting injectable naltrexone is being developed to improve outcomes by enhancing patients' compliance with therapy through reduced dosing frequency and better tolerability. Long-acting injectable naltrexone makes use of advanced drug-delivery technology that

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provides therapeutic amounts of drug with just one intramuscular injection per month and thereby eliminates the need for daily dosing. In addition, the long-acting formulation provides relatively constant naltrexone blood levels over a one month interval as distinguished from the more widely fluctuating blood levels associated with daily oral dosing. As stable blood levels may be less likely to be associated with adverse events than frequently fluctuating blood levels, the new form could be better tolerated than the oral form (See Figure 1).

The pharmaceutical firm Alkermes, Inc. is developing one version of long-acting injectable naltrexone and the drug is not yet approved by the US Food and Drug Administration (FDA) for the treatment of alcohol dependence in the United States. A primary investigator in the pivotal Phase III study testing the safety and efficacy of long-acting naltrexone, Garbutt has presented data at major medical meetings including the 2004 American Society of Addiction Medicine, the 2004 Research Society on Alcoholism, and the 2004 International Society for Biomedical Research on Alcoholism. Garbutt considers the most recently completed placebo-controlled, double-blind study, which involved 624 alcohol-dependent subjects, to be the most informative. The study included three groups of subjects—one receiving long-acting naltrexone 190 mg, the second receiving long-acting naltrexone 380 mg, and the third receiving placebo once per month for 6 months. Subjects also received a low-intensity form of psychosocial therapy known as BRENDA and could attend Alcoholics Anonymous meetings.

The study employed an innovative way of measuring the effectiveness of treatment. Many past clinical trials of pharmacotherapies for alcohol dependence assessed relapse to heavy drinking as a primary outcome. In those trials, a relapse was considered a treatment failure, and a patient was considered to have failed treatment after one relapse. Garbutt notes that this method of measuring effectiveness is not a sensitive way to assess the impact of treatment over time. "A drug that does not prevent *all* relapses can still be effective at reducing the *number* of relapses over time or at reducing the amount of alcohol ingested during relapses. Traditional means of assessing the effectiveness of pharmacotherapy for alcohol dependence frequently do not take into account the latter possibilities," says Garbutt. In an attempt to overcome these shortcomings, the trial of

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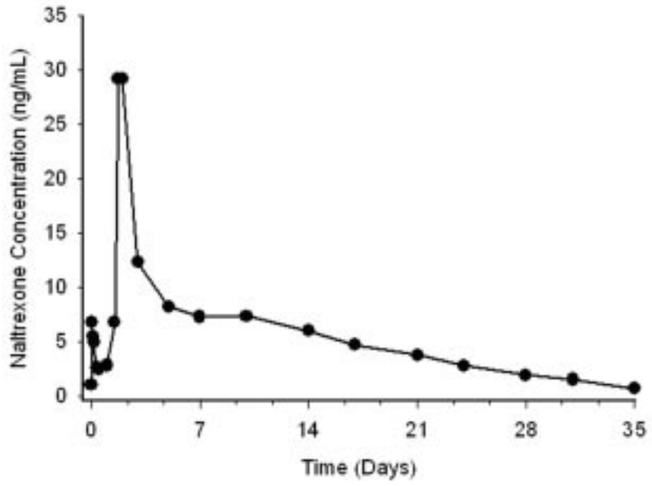

Figure 1. Steady state naltrexone plasma concentration versus time in a representative individual following the fourth consecutive dose of Vivitrex® 380 mg (Q28 days). [Data courtesy Alkermes Inc.]

James C. Garbutt, M.D.

Professor of Psychiatry, UNC School of Medicine; **Medical Director**, Alcohol and Substance Abuse Program; **Faculty**, Bowles Center for Alcohol Studies

Education

Staff Fellowship, 1980, National Institute of Mental Health, Bethesda, Maryland; Psychiatry Residency, 1978, University of North Carolina at Chapel Hill; M.D., 1975, Univof Illinois Medical Center, Chicago, IL; B.A., 1971, Honors in Biology, University of Illinois, Urbana, IL

Recent Publications

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Web page: http://www.med.unc.edu/alcohol/faculty/GarbuttJC/Garbutt.htm

The Director's Column

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

What a wonderful and exciting time to be an alcohol researcher. This issue of the Centerline features two outstanding faculty who are at the cutting edge of science dedicated to making the lives of humans healthier and happier. Dr. J.C. Garbutt is leading our efforts to directly improve the success rates in the treatment of addiction, particularly alcoholism. We know that if people stay in treatment longer, they will do better and are more likely to have healthy positive lives in recovery. We know that treatment works, it takes longer in some folks, and does not work for everyone the first time, but it does work and it works better for those who stay in treatment. One of the fascinating things about pharmacotherapy not often emphasized is that it reduces the drop out rate from clinical treatment and keeps patients in therapy longer. This may be related to reducing relapse and craving, but ultimately one important aspect is to improve the time in treatment and recovery. Current pharmacotherapies are based on animal models that suggest non-addictive drugs could change drug-seeking and consuming behavior. Alcoholism is not homogeneous and the more approaches we have for clinicians to treat this complex disease, the better treatment will be for each and every individual. Animal studies over twenty years ago showed that opiate antagonists, which are not addictive, could decrease alcohol drinking and led to the current use of naltrexone to treat alcoholism. The new slow release formulation will likely improve on the single daily dose first published for human therapy 10 years ago. I don't know where we will be in the next 10 years, but I think we are moving faster with many more new opportunities to improve treatment of alcoholism.

Dr. Tom McCown uses cutting edge gene delivery technology to specifically change gene expression in discrete areas of brain. These studies help us understand how gene expression modulates behavior as well as providing a foundation for potentially new therapeutic approaches. I predict these studies will broaden to treatment for addictions and provide a number of new and novel treatment approaches. This is why it is truly a wonderful and exciting time to be an alcohol researcher.

Continued from previous page

long-acting injectable naltrexone employed multiple time to event-rate analysis. This approach, not previously routinely applied in alcohol-dependence trials, examined the pattern and number of relapses to heavy drinking over the course of the 6-month trial. The results show that patients receiving the higher dose of long-acting injectable naltrexone compared with patients receiving placebo had significantly fewer cumulative heavy drinking days and the effects were most notable in men.

Asked whether or not he views these findings as being clinically significant, Garbutt speaks enthusiastically: "Very much so. Over a 6-month period, male patients treated with naltrexone had one less month of heavy drinking than placebo-treated patients. That one month free of heavy drinking may translate into lower risks to physical and mental health, lower incidences of drinking-associated interpersonal and family problems, and fewer problems at work. The event-rate analysis proved to be a powerful way to show the impact of pharmacotherapy."

Garbutt also views the study as a success according to the criterion of improved compliance. Approximately two thirds of patients completed all 6 months of the study and received treatment as directed. The injections were generally well accepted and well tolerated. These results suggest that, as intended, the long-acting form of naltrexone can provide a physical method to enhance compliance that is agreeable for most patients and can eliminate the necessity of having to make the day-to-day decision of whether to take oral medication—a significant source of compliance problems for individuals with alcoholism.

In addition to studying long-acting injectable naltrexone, Garbutt is investigating other compounds at earlier stages of human testing than naltrexone. Garbutt names aripiprazole and baclofen as among the compounds under investigation. Aripiprazole acts on the brain's dopamine system, which appears to be involved in the mediation of craving and the desire to drink. Baclofen acts on the brain's GABAergic system, which is another important system in mediating alcohol intake, loss of control, and mood. "We're getting better," says Garbutt. "We are better at targeting brain systems important in alcohol dependence, better at conducting clinical studies, and better at choosing appropriate outcome measures. Alcohol dependence is a complicated problem, and there is no magic bullet. However, it's exciting that, after a long period in which few medicines were available for alcohol dependence, we now have pharmacotherapeutic options proven to help—and more are on the way."

Post-Doctoral Fellowships Now Available!

Our Center is offering post-doctoral fellowships in a multidisciplinary training program funded by NIAAA. 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 Information, visit www.med.unc.edu/alcohol/postdoc.htm.