

Transdisciplinary Tobacco Use Research Centers: Developmental and Pilot Research

by Glen Morgan

The Transdisciplinary Tobacco Use Research Centers (TTURCs) initiative began in 1999 with seven academic institutions awarded 5-year grants by the National Cancer Institute (NCI) and the National Institute on Drug Abuse (NIDA).

A key component of the TTURC RFA was that applicants were required to include a program that would promote developmental and pilot research to facilitate new collaborations and the opportunity to pursue challenging ideas. The purpose of these pilot funds was to stimulate projects that take maximum advantage of new research opportunities. Such projects could be collaborative among scientists within one or more TTURCs, or with scientists outside the TTURC environment. Furthermore, applicants were instructed to propose an institutional review process that selected pilot projects for funding which represented the most innovative and transdisciplinary ideas and which were likely to have the greatest impact on reducing the burden of tobacco use and its consequences.

The developmental/pilot program was seen as critical in allowing expeditious exploration of novel research questions, especially those that might arise in the progression of the major projects. Interdisciplinary and cross-center collaboration increased with the maturation of the TTURC centers and the initiative as a whole, and provided a catalyst for creative new scientific directions. The streamlined within-center application and review process allowed researchers to rapidly respond to new opportunities. This, in turn, produced important work that could be leveraged into an R01 (or traditional research grant) application.

Outcomes of the TTURC pilot projects are presented in this issue of the Networker.

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Pilot Projects Expand Scope of Work and Increase Research with Tobacco Focus

by Jeanne Mettner

In 1999, the University of Minnesota Transdisciplinary Tobacco Use Research Center (UMN) launched its Pilot Projects program as a means of attracting new investigators and novel approaches to the field of transdisciplinary tobacco research and for broadening the scope of the work at the TTURC. Additional aims were 1) to provide training for these investigators to facilitate their expansion into the field of transdisciplinary tobacco use research and 2) to enhance the UMN TTURC's capacity in specific targeted areas by recruiting collaborators with needed expertise.

The past five years have witnessed active and productive work within this program. The UMN TTURC has funded 15 pilot projects, representing investigators from 10 departments, 6 of whom were new to tobacco research. Projects ranged from molecular biology to public policy. These pilot projects have already resulted in significant successes. For example:

- Natalia Tretyakova, Ph.D., received an R01 grant to continue her work on identifying target compounds for chemoprevention of lung cancer in smokers.
- Paul Pentel, M.D., received an R01 to continue studying the effectiveness of a nicotine vaccine on nicotine transfer and effects in the fetus.
- Edward Janoff's, M.D., successful project, which explored the impact of smoking on mucosal immunity and pneumonia vaccine responsiveness, allowed him to incorporate a new tobacco research direction into an already existing R01 grant.
- Jesse Mason, a graduate student, used his pilot data regarding racial differences in nicotine metabolism to receive funding for a TTURC supplement to expand this work.

Perhaps the most compelling testament to the success of the program is that the results of some pilot studies themselves were worthy of peer-reviewed publication. In 2001, for example, Deborah

Henrikus, Ph.D., studied the preferences and practices among renters regarding smoking restrictions in apartment buildings. This work demonstrated that the majority of renters in a first-ring suburb of Minneapolis were exposed to unwanted secondhand smoke and wanted no-smoking policies for apartments that would eliminate this exposure. The results of this work were published in 2003 (*Tobacco Control* 2003; 12(2):189-94).

Information yielded from UMN TTURC's pilot studies has also contributed to the robust pool of evidence-based data that is often critical for shaping thoughtful public policy. In April 2004, Ozlem Tulanay, M.D., completed her study on environmental tobacco smoke in hospitality venues. She found that bar and restaurant employees had significant increases in levels of nicotine, cotinine (a biomarker for nicotine), and NNAL (a biomarker for a potent lung carcinogen) on working days versus nonworking days. Tulanay and her colleagues concluded that "the results of this study reinforce the importance of smoking bans in restaurants and bars to protect employees' health." The results of her work have been written up in a peer-reviewed article, currently in press with the journal *Cancer Epidemiology, Biomarkers and Prevention*.

As a result of the overall success and productivity of past and current UMN TTURC pilot studies, the number of investigators focusing on tobacco research has increased at UMN and the range of interests represented has significantly expanded. Not surprisingly, the Pilot Projects program continues with vigor in TTURC II. For the next five years, within this program, three to five pilot projects will be funded each year at a level of up to \$20,000 for one year. This represents an increase from the previous five years, during which three grants were funded each year at a level of up to \$10,000 for one year.

Pilot Research Examines the Effects of Nicotine on the Brain

by Louri Groves

The University of California, Irvine (UCI) TTURC has funded 17 pilot grant awards, across a diversity of disciplines. Of the 17 projects, the center awarded funding to four junior researchers and various senior faculty, allowing them to explore new research directions.

Two junior researchers have since applied for independent research support using pilot data obtained with the award, while other awards have led to several subsequent grant applications and to two major awards.

Diane O'Dowd, Ph.D., UCI associate professor of Anatomy & Neurobiology, received a five-year grant from NIDA to further her studies on how a variety of environmental factors such as exposure to specific chemicals, including nicotine, can influence information transfer between neurons from the brains of fruit flies (*Drosophila*).

Jogeshwar Mukherjee, Ph.D., UCI associate professor of Psychiatry & Human Behavior, used his pilot funding to initiate the development of Nifrolidine and to help establish a laboratory at the UCI Brain Imaging Center. Nifrolidine, a selective binding agent, identifies specific areas of the brain responsible for decision-making, learning, and memory. He developed Nifrolidine to measure a subtype of nicotine receptors in the living brain by using an imaging technique, positron emission tomography, more commonly known as PET scans. After proving the drug's ability to provide reliable data, Mukherjee believes the drug will have implications for other conditions, such as Alzheimer's and schizophrenia. In addition, he successfully competed for a three-year Department of Energy grant to further his studies and applied for a patent invention disclosure on Nifrolidine.

One award to John Whiteley, Ph.D., professor of Social Ecology, Environmental Analysis & Design, was used to provide knowledge and technology from the UCI group to tobacco researchers in Russia. "This intellectual transfer has led to the submission of funding applications by our Russian colleagues,"

Whiteley said. "Unilever, a major international corporation, recognized the need for health promotion and recently granted an award to our colleagues."

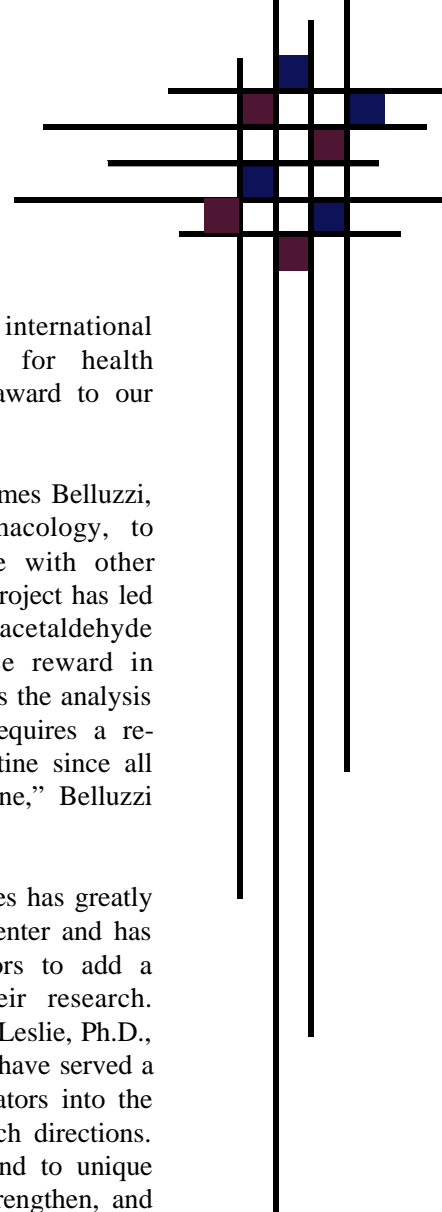
Initial funding was also awarded to James Belluzzi, Ph.D., adjunct professor of Pharmacology, to examine the interaction of nicotine with other constituents of tobacco smoke. This project has led to the subsequent discovery that acetaldehyde synergizes with nicotine to enhance reward in adolescence. "The results complicates the analysis of smoking in animals because it requires a re-evaluation of animal studies on nicotine since all research has focused on nicotine alone," Belluzzi said.

The participation of these pilot grantees has greatly enriched the intellectual life of the Center and has encouraged a number of investigators to add a nicotine and tobacco focus to their research. According to Center Director, Frances Leslie, Ph.D., professor of Pharmacology, the grants have served a critical role in bringing new investigators into the Center and in stimulating new research directions. "We also used the program to respond to unique opportunities as well as to bridge, strengthen, and extend our main research projects," Leslie said.

Over 55 junior and senior UCI investigators from 16 departments across 8 schools actively participated in various tobacco research projects.

Each pilot project was required to meet at least one of the following criteria:

- 1) Bring new faculty into the center
- 2) Foster development of junior faculty
- 3) Develop new directions for the center
- 4) Create and capitalize on new opportunities for the center
- 5) Allow investigators to gather preliminary data for subsequent grant applications



Prevention of Smoking Relapse Examined in Pilot Research

by Gloria Meyer

From examining rat brains to interviewing pregnant women, the University of Wisconsin (UW) TTURC pilot studies demonstrate a variety of content and methodology in their focus on preventing relapse to smoking.

Relapse prevention strategies among pregnant women who quit spontaneously, were examined in a pilot study conducted by Pamela Pletsch, Ph.D., R.N., now at the University of North Carolina Department of Nursing. In this study, in-depth interviews were used to assess the personal environmental factors associated with abstinence and relapse among pregnant women who spontaneously stopped smoking during their pregnancy.

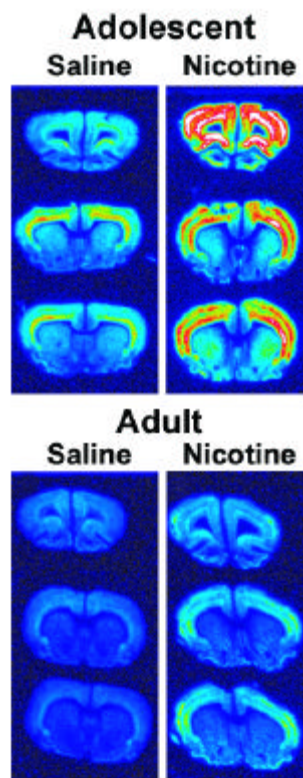
One key finding of this study was a change in women's perceptions of the taste and smell of tobacco during pregnancy. Women reported that they lost their taste for cigarettes, and even developed an aversion to smoking. Most believed this change was related to being pregnant. One woman said, "I would light a cigarette and then just not have the taste or it would make me sick." Another likened the taste to "bug spray."

Findings from this study were presented at the Southern Nursing Research Society Conference in Orlando, FL, in February of 2003. A manuscript has been submitted to a scientific journal for review. Pletsch intends to expand the research in this pilot project by surveying 300 pregnant smokers participating in a cessation trial. She has also applied for a grant based on the taste change findings.

In another project, Charles Landry, Ph.D., studied the influence of nicotine on behavior and gene expression in adolescent rodents. One of the questions Landry, Department of Psychiatry, UW Medical School, and his colleagues Ann Kelley and Terri Schochet asked was if adolescent rats respond differently than adults to an environment previously

associated with nicotine. Interestingly, although adolescent and adult rats sensitize to repeated nicotine treatments in a similar way, unlike adults, adolescent rats fail to "condition" (respond with an increase in locomotor activity) to an environment where they had previously received nicotine.

To begin to understand the bio-chemical basis of this difference, Landry and colleagues went on to treat adolescent and adult animals with nicotine and then examine changes in the expression of plasticity-related genes. One observation they made was that a single dose of nicotine caused a dramatic elevation in the synaptic protein, arc, in specific regions of the adolescent prefrontal cortex (PFC; see figure). These results suggest that adolescent rats may be neurologically vulnerable to nicotine in regions of the brain, like PFC, that are critical for emotional regulation and decision making.



From this work, the article "Differential behavioral effects of nicotine exposure in adolescent and adult rats" was published in *Psychopharmacology*, (April, 2004). Another article entitled "A differential expression profile of arc mRNA and other plasticity-related genes is induced by nicotine in adolescent and adult rat forebrain" is under revision in the *Journal of Neuroscience*. In addition, an R01 grant application based on data obtained from the TTURC pilot study and entitled "Nicotine and Gene Expression in Adolescent Brain" was funded in

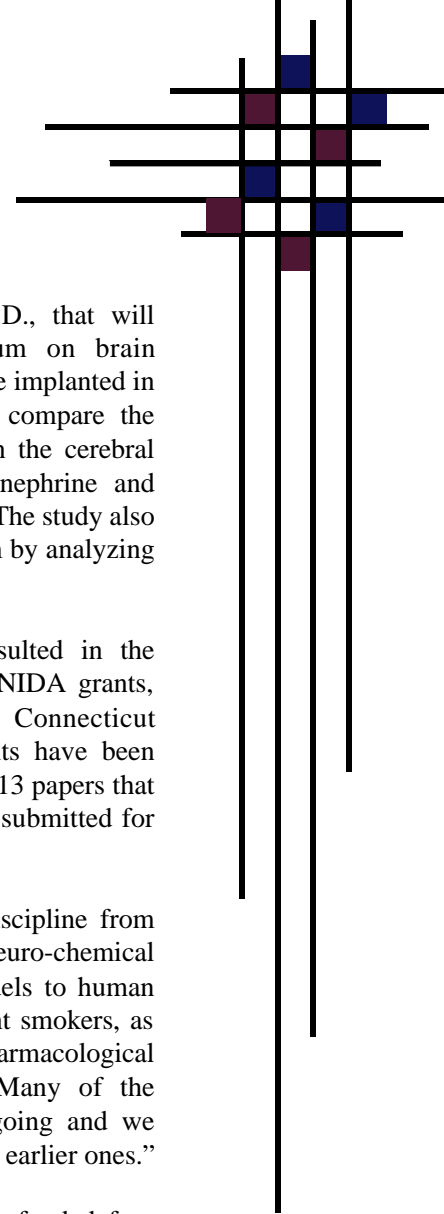
October 2004.

An additional pilot study, "Smoking and stress response," by John Curtin, Ph.D., Department of Psychology, yielded interesting data on affective characteristics of dependent versus occasional smokers. Gender differences in stress response recovery and decreases in positive affect after stressor exposure were found. These results are being

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Successful Pilot Work Across Scientific Disciplines

by Pem McNerney



The pilot project program at the Yale TTURC has served to fulfill numerous objectives. It has allowed the group to explore new research technologies, it has provided important information on potential pharmacological and behavioral treatments, and it has attracted talented investigators to the group.

The program also has resulted in the submission of several R01s, the publication of numerous papers and the development of additional research.

“We have been highly successful in increasing the number of tobacco investigators over the past four and a half years,” said Yale TTURC Center Director Stephanie O’Malley, Ph.D. “At the same time, the program has added significantly to the body of research produced by our group.”

During the first phase of the Yale TTURC, 13 projects were funded. Results from one of the most successful, “Selegiline for Smoking Cessation: A Pilot Study,” by Tony George, M.D., resulted in a funded NIDA R01 application to conduct a large-scale clinical trial that is ongoing. Results from the pilot work of Sherry McKee, Ph.D., “Modeling the Effect of Alcohol on Relapse to Tobacco” contributed significantly to McKee’s TTURC II project, “Modeling Smoking Lapse Behavior for Drug Development.”

O’Malley said researchers are encouraged to design projects that reflect their unique interests and expertise, as well as the goals of the Yale TTURC. One such project, she said, is the pilot project being

conducted by Idil Cavus, M.D., Ph.D., that will examine the effect of nicotine gum on brain neurochemistry by using probes that are implanted in the brain. The study is designed to compare the effects of nicotine gum to placebo on the cerebral release of glutamate, GABA, norepinephrine and dopamine using in vivo microdialysis. The study also will examine the effect of nicotine gum by analyzing intracranial EEG recordings.

To date, the pilot projects have resulted in the submission of seven applications for NIDA grants, one to NIAAA, and one to the Connecticut Department of Public Health. Results have been incorporated into 14 presentations and 13 papers that have been accepted for publication or submitted for revisions.

“The pilot projects have ranged in discipline from physiological, molecular biological, neuro-chemical and behavioral studies in animal models to human imaging studies in adult and adolescent smokers, as well as human biobehavioral and pharmacological treatment studies, O’Malley said. “Many of the recently funded projects are still ongoing and we expect they will be as productive as the earlier ones.”

O’Malley said TTURC II has already funded four pilot projects. They include “Molecular Regulation of Nicotine Reward by Beta 2 Nicotinic Receptors,” “Framing Tobacco Messages to Target Adolescent Smokers,” “Naltrexone & Bupropion to Stop Smoking with Less Weight Gain,” and “The Role of Expectancies in a Clinical Trial of Selegiline.”

Prevention of Smoking Relapse: Continued from page 4

prepared for publication. In addition, further research in this area will be conducted as part of the second round of TTURC studies.

A fourth pilot, “Impact of withdrawal on nicotine expectancy and response: an fMRI investigation of regional brain activity,” Richard Davidson, Ph.D., Department of Psychology, is ongoing. The goal is to show how much certain brain structures related to reward anticipation are influenced by manipulations

designed to heighten smoking motivation. Findings may shed light on brain processes involved in perpetuating smoking behavior and may suggest potential therapies.

It seems that successful pilots grew out of an intense interest by the researchers, who were able to build upon previous research in other areas and apply it to tobacco use.

Pilot Research Facilitates Collaboration with China

by Jeff Baskin

USC's Transdisciplinary Tobacco Use Research Center and its successor, the Pacific Rim Transdisciplinary Tobacco & Alcohol Use Research Center (PR TTURC), have focused on the cultural, social, psychological, environmental, and, now, genetic factors affecting tobacco use and prevention among youth in California, Hawaii and Mainland China. The aim of the first TTURC's seven pilot projects was to support the research mission of the Center while encouraging doctoral students, new investigators, and established researchers to expand into transdisciplinary tobacco use research.

Of the seven pilot studies, the China Seven Cities Study (CSCS) has had the largest impact. Headed by PR TTURC director C. Anderson Johnson, CSCS is a longitudinal study focusing on tobacco use and other health-related behaviors amid rapidly changing social, cultural and economic conditions in the People's Republic of China. A collaborative effort, it joins U.S. researchers with the Chinese Center for Disease Control and Prevention, Peking University, and the city CDCs from the regionally diverse cities of Chengdu, Hangzhou, Harbin, Kunming, Qingdao, Shenyang, and Wuhan. Participating in the TTURC I U.S. research team were members of the TTURCs at Brown University, University of Minnesota, University of California at Irvine, University of Pennsylvania/Georgetown, and Yale University.

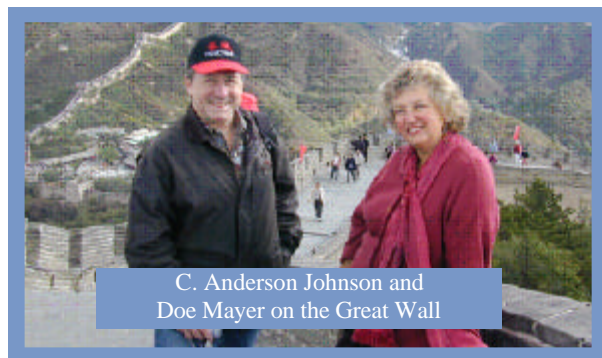
Among the study's accomplishments:

- Trained Chinese health leaders and academicians in new techniques in public health research;
- Provided training to doctoral and post-doctoral students in TTURC's parent organization, the Institute for Health Promotion & Disease Prevention Research Center; and,
- Yielded 17 papers in press, submitted for publication, or in preparation.

CSCS findings were the focus of two major conferences co-hosted by the USC TTURC as well as a major symposium at the 2004 Conference of the Asia-Pacific Academic Consortium for Public Health

(APACPH) in Brisbane, Australia, and a workshop at the 2003 World Conference on Tobacco or Health in Helsinki, Finland.

Moreover, CSCS became a centerpiece of the successful grant proposal for the new PR TTURC, which has led to even closer collaborations with researchers and public health providers outside USC. Now, SRI International, an independent, nonprofit research institute headquartered in Menlo Park, California, and the municipal Centers for Disease Control in the Chinese cities of Chengdu, Qingdao, and Wuhan are full partners with USC in the Center's transdisciplinary research.



C. Anderson Johnson and
Doe Mayer on the Great Wall

Following are the other pilot projects at USC TTURC:

- Psychosocial Predictors of Smoking Across Cultures (PI: Elahe Nezami, Ph.D.)
- Egyptian Cultural Values and Adolescent Smoking Study (PI: Sondos Islam)
- Social Resources and Smoking Among Hispanic Youth (PI: Lourdes Baezconde-Garbanati, Ph.D.)
- Race/Ethnicity & Student Tobacco Use (PI: Thomas Hanson)
- Intergenerational Pathways of Tobacco Use (PIs: Merrill Silverstein, Ph.D.)
- Quality of Time Use & Adolescent Smoking (PIs: Ruth Zemke, Ph.D., & Wenchen Qu,???)
- Smoking Behavior and Influential Factors Among Private School Students in Wuhan (PI: Dexin Zhang, ???)

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