Colorado Tobacco Research Program

2003 Annual Report

to the

Colorado Department of Public Health and Environment

Colorado Tobacco Research Program • University of Colorado, CB 051 SYS • Boulder, Colorado 80309-0051
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Executive Summary

The Colorado Tobacco Research Program (CTRP) is charged with conducting a research grant program that supports the people of Colorado by directly addressing the mental health, educational, cessation, prevention and illness-related needs caused by tobacco and substance abuse within the state. To meet this objective, CTRP seeks to address the challenges of identifying, funding, and disseminating new and relevant developments in tobacco- and substance abuse-related research. To disseminate findings from its sponsored research, CTRP also communicates and collaborates with other tobacco control programs, such as the State Tobacco Education and Prevention Partnership in Colorado.

CTRP appropriations for FY 2003 were originally slated to be approximately $7.9 million per SB 00-071. However, in May 2003, due to state budget shortfalls, the State Legislature's Joint Budget Committee reduced CTRP allocations for FY 2003 by 62% to $3 million; all of which were dedicated to new projects beginning July 1, 2003. Also in May 2003, SB 02-282 stipulated that CTRP appropriations for FY 2004 would be diverted to the state General Fund, and HB 03-1256 specified that CTRP appropriations from FY 2005 onward would be diverted to the State's capital development fund to support interest payments on the Certificates of Participation for the University of Colorado Health Sciences Center at Fitzsimons campus. Due to the elimination of future annual appropriations to the tobacco research fund, the University of Colorado will conclude its administration of CTRP once all ongoing projects are completed by June 2005.

For the 2003 funding cycle, CTRP emphasized the following research priorities:

- Research that addresses specific Colorado needs with regard to tobacco control among underserved and/or vulnerable populations in all areas of investigation.
- Studies examining all aspects of secondhand smoke exposure.
- Racial, ethnic, age and/or gender-based differences in tobacco interventions and in smoking-related diseases.
- Biomedical research that addresses the health needs of current and/or former smokers, especially translational and clinical studies to develop and validate novel treatments, prevention strategies, validation of early diagnostics, as well as development of more relevant animal models for tobacco-related diseases or addiction.
- Research focused on tobacco-related heart disease, lung illnesses and/or cancers.
- Research focused on prevention of tobacco use across the tobacco control continuum, especially studies of environmental factors that influence initiation of tobacco use, including the role of the tobacco industry.
- Research on tobacco, alternative tobacco / nicotine delivery devices, and tobacco smoke constituents in addition to nicotine that contribute to tobacco-related diseases and to addiction as well as potentially reinforcing the actions of nicotine.
- Evaluative research that focuses on the impact of state and local public policies and programs, particularly among specific populations.
- Studies that use Colorado's data collections (e.g., 2002 Tobacco Attitudinal Baseline Survey) for secondary data analysis.

In 2003, CTRP awarded

- 14 grants
- for $3.0 million
- at six Colorado institutions

Introduction

This is the fourth Annual Report of the Colorado Tobacco Research Program to the Colorado Department of Public Health and Environment, covering the period of July 1, 2002 through June 30, 2003 as mandated in Senate Bill 00-071, section 11, 23-20-208.

The Colorado State Legislature created the tobacco research fund as part of Senate Bill 00-071, which determined how the State of Colorado's share of the national tobacco settlement funds would be spent. The bill allocated up to 8% of the monies received annually for the establishment of a comprehensive clinical, basic science, mental health, and evaluative research grant program that would serve Colorado's tobacco- and substance-abuse-related health care needs. SB 00-071 ensured that the research grant program supported the people of Colorado by directly addressing the mental health, educational, cessation, prevention and illness-related needs caused by tobacco and substance abuse within the state.

To implement the research program, the State Legislature assigned the Office of the President of the University of Colorado (CU) the duty of administering the Colorado Tobacco Research Program (CTRP). Within the CU Office of the President, the Vice President for Academic Affairs and Research thus created CTRP, with the charge to award research grants based on scientific merit and relevance to the Program's mission in an open, competitive manner. As stipulated by SB 00-071, funding for administrative expenses is limited to five percent of the monies appropriated annually to CTRP. SB 00-071 also directed the Governor of the State of Colorado to establish a Scientific Advisory Committee to counsel the University on the direction, scope and progress of CTRP. Appointed by the Governor, Committee members represent voluntary health organizations dedicated to the reduction of tobacco use, experts in the fields of biomedical or social/behavioral research, representatives from research universities and institutions focused on tobacco-related issues affecting children and youth, and members of medical or health organizations. The Scientific Advisory Committee primarily develops the strategic objectives and priorities of CTRP, facilitates coordinated efforts between the Program and other stakeholder entities focused on reducing tobacco use and tobacco-related disease in Colorado, participates in Program evaluation, and makes the final recommendations on which research applications should be funded.

After three funding cycles, CTRP is reporting on a total of 41 active research projects as well as four completed projects. These ongoing and completed studies are contributing to our knowledge about the etiology, pathogenesis, diagnosis and treatment of tobacco- and addiction-related diseases and the development, implementation, evaluation, and dissemination of existing or novel approaches to tobacco control and substance abuse education. Individual investigators from multiple institutions across the state are embarking on a broad portfolio of research, ranging from prevention and cessation of tobacco use to improved diagnoses and treatments that will reduce tobacco-related morbidity and mortality. By providing more than $15.9 million to fund these completed, ongoing and new projects, CTRP remains committed to reducing the physical and mental health impact, and the corresponding economic burden, of tobacco-related diseases within the state.

2003 initially represented a year of promise for CTRP, as the Program was slated to receive approximately $7.9 million, its largest annual appropriation to date. However, the state was enduring an economic downturn, which created a severe budget shortfall. In November, coinciding with the annual release of CTRP's Call for Applications, the Governor's proposed budget was released and, among other measures, called for a 50% reduction in CTRP's appropriation for FY 2003. Despite the published availability of the largest appropriation in CTRP's history, Colorado researchers responded pessimistically to news of this potential cut, as the opportunity for funding was perceived to be significantly lower than in previous cycles. CTRP received only 35 applications for grants in January 2003, down from 48 the year before. Ultimately, per SB 03-190 and SB 03-282, CTRP FY 2003 appropriations were reduced by 62%, leaving $3 million available for new awards this year. Due to the reduced number of submissions coupled with the diversion of FY 2003 appropriations to the state's General Fund, CTRP's "payline" (the percentage of submitted applications approved for funding) was 40%, comparable to previous funding cycles.

Looking forward, it is unlikely that CTRP will be able to continue fulfilling its mandate as originally identified by SB 00-071. In May 2003, SB 02-282 stipulated that CTRP appropriations for FY 2004 would be diverted to the state General Fund, and HB 03-1256 specified that CTRP appropriations from FY 2005 onward would be diverted to the State's capital development fund to support interest payments on the Certificates of Participation for the University of Colorado Health Sciences Center at Fitzsimons campus. Despite the elimination of annual state appropriations to support either future awards or administration of the Program, the University of Colorado is committed to overseeing all active projects through their conclusion (including those initiated in FY 2003). Nevertheless, in the absence of future administrative revenues as provided per SB 00-071, the University will have to sunset CTRP once all currently ongoing projects are completed by June 2005.

General Reporting Requirements

As specified by the Colorado State Board of Health, "Tobacco Settlement Monitoring and Reporting Rules" (available via www.cdphe.state.co.us/op/regs/boardofhealth/101402tob.pdf), each tobacco program shall annually submit to the department a report which, at a minimum, includes the following information:

(a) The amount of tobacco settlement moneys received by the program for the preceeding fiscal year.

Colorado Tobacco Research Program FY 2003 annual appropriation: **$3,000,000**

(reflects a reduction of $4,918,729 million from initial appropriation as authorized by SB 03-190 and SB 03-282).

(b) A description of the program, including the program goals, population served by the program, the actual number of people served, and the services provided.

CTRP Goals: Implement a grant program to support mental health research and basic scientific, clinical, and evaluative research into tobacco and substance abuse related disease, illness, education, evaluation, cessation, and prevention.

Population served: All Coloradoans. The actual number of people served by ongoing CTRP research projects will be dependent on their relative outcomes, the successful implementation of scientific findings into "best practices" of existing and future tobacco control programs, and future studies designed for translational and clinical research into novel diagnoses and treatments for tobacco-related diseases.

Services provided: CTRP provides research funds to investigators at all universities, colleges, research institutes, and other nonprofit institutions in Colorado via a grant application process.

(c) An evaluation of the operation of the program, which includes the effectiveness of the program in achieving its stated goals.

Internal evaluation process
As directed by SB 00-071, the Governor-appointed Scientific Advisory Committee primarily develops the strategic objectives and priorities of CTRP, facilitates coordinated efforts between the Program and other stakeholder entities focused on reducing tobacco use and tobacco-related disease in Colorado, participates in Program evaluation, and makes the final recommendations on which research applications should be funded. At each of their quarterly meetings, the Committee reviews the progress of ongoing CTRP-funded projects, assesses the need for changes to the program's Research Priorities as determined by research findings and emerging trends in tobacco control and substance abuse, and implements new directives for the program via revision of the annual Call for Applications. To ensure that research sponsored by CTRP meets programmatic goals, the Committee bases its recommendations on the scientific merit of the proposed research as determined by peer review and on programmatic priorities, including but not limited to, the extent to which a proposal addresses CTRP's research priorities.

External evaluation process

In 2003, CTRP contracted with the University of California Tobacco-Related Disease Research Program (TRDRP) to review CTRP grant applications. Established in 1989, TRDRP operates a grant evaluation program modeled after that of the National Institutes of Health (NIH), utilizing expert reviewers from all states (including Colorado) but excluding California. Relevant applications submitted in response to the 2003 CTRP Call for Applications were assigned by TRDRP staff to a study section comprised of evaluators appropriate for the scientific discipline and subject matter. CTRP uses the University of California review program for two reasons: scientific excellence and fiscal responsibility. The TRDRP conducts an NIH-type evaluation process independently of CTRP; there is no other entity either in Colorado or nationally that offers this evaluation service. Using the TRDRP was a fiscally prudent alternative to creating an independently designed review process, which would otherwise have cost CTRP more money annually than it has in its administrative budget. Outsourcing of the application evaluations also ensured that CTRP funded only those applications deemed to be meritorious by a rigorous peer review process as mandated by SB 00-071.

(d) The costs incurred by each program that receives settlement moneys, including but not limited to the amount and justification of administrative costs incurred by the agencies that implement the program.

$3,000,000	FY 2003 appropriations to the Colorado Tobacco Research Program
$2,850,000	Expended and/or encumbered for new awards in FY 2003
$ 150,000	Administrative costs incurred for FY 2003
$ 0	Returned to the Tobacco Settlement Trust Fund for FY 2003

Specific Reporting Requirements

Senate Bill 00-071 specifies how the University of Colorado shall provide information annually regarding the Colorado Tobacco Research Program. Section 23-20-208 states:

"The Office of the President shall submit to the Department of Public Health and Environment a report concerning the research grants awarded pursuant to the research program. The department shall include said report in the annual report of programs that are funded by moneys received pursuant to the Master Settlement Agreement prepared pursuant to Section 25-1-108.5(3), C.R.S. The report shall include the following information for each institution and organization that receives grant awards:

(a) Award allocation (the number and dollar amounts of research grants received through the Research Program, including the amount allocated to indirect costs)

(b) The subjects of research grants by academic discipline

(c) The relationship between state and federal funding for tobacco- and substance-abuse-related research

(d) The relationship between each project and the overall strategy of the research program

(e) A summary of research findings

(f) Any recommendations for future Program directions."

In Sections (a), (b) and (c), these items are provided in aggregate form for all grants currently supported by CTRP funds. Then, the information is presented separately for each award in Section (d), in which every grant funded to date is listed, including the name of the Principal Investigator, the title of the research project, the area of research, the term of the project, and the total dollar amount of the award. Finally, for Section (e), abstracts (summaries of results) from the annual progress reports are reproduced.

Summary Data for 41 Ongoing Grants Made to 9 Institutions

(a) Award Allocation

The following table details the allocation of funds by institution
(*not including awards terminated prematurely or completed in previous fiscal years*):

Table 1

Allocation of CTRP Funds for Active Grants by Institution

Institution	Number of Grants (% of total)	Grant Award Amount		
		Total Grant Award *(% of total)*	***Direct Costs***	***Indirect Costs***
American Lung Association of Colorado	1 (2)	$58,160 (0.5)	$58,160	$0
Colorado School of Mines	1 (2)	$366,459 (3)	$242,614	$123,845
Colorado State University	4 (10)	$927,939 (7)	$678,236	$249,703
Cooper Institute, Denver	1 (2)	$568,320 (4)	$363,026	$205,294
National Jewish Medical & Research Center	7 (18)	$2,702,897 (21)	$1,871,753	$831,144
University of Colorado at Boulder	9 (22)	$3,289,659 (25)	$2,332,918	$956,741
University of Colorado at Colorado Springs	1 (2)	$137,449 (1)	$99,963	$37,486
University of Colorado at Denver	2 (5)	$682,480 (5)	$501,647	$180,833
University of Colorado Health Sciences Center	15 (37)	$4,255,209 (33)	$3,060,340	$1,194,869
Totals	**41 (100)**	**$12,988,572 (100)**	**$9,208,657**	**$3,779,915**

(b) The Subject of Active Research Grants by Academic Discipline

Table 2 details the current distribution of CTRP awards according to research area.

Table 2

Award Distribution – Active Grants by Research Area

Research Areas	Number of Awards	Amount Funded (% of total)
Disease Diagnosis & Treatment	19	$6,064,121 (46)
Nicotine Addiction	5	$1,461,286 (12)
Prevention and Cessation	13	$4,320,585 (33)
Mental Health	3	$1,084,420 (8)
Policy and Public Health	1	$ 58,160 (1)
Total	**41**	**$12,988,572 (100)**

The information provided in Table 2 can be restated in the following way: through the first three cycles of CTRP funding, slightly less than half of the awarded funds are supporting nineteen studies that focus on tobacco-related disease processes, ranging from basic biological studies of

the molecular and cellular changes that are critical to the initiation of disease, the development of new or refined diagnostic approaches to identify disease progression, and on potential therapies and/or novel drug delivery techniques. One-third of the awarded funds are dedicated to thirteen projects that center on the social and biobehavioral factors underlying why individuals start to smoke, and on the development of interventions to counter youth susceptibility to tobacco use and substance abuse. Twelve percent of the award monies support five projects that are investigating the underlying physiological mechanisms that may predispose individual susceptibility to nicotine or play key roles in the progression of addiction. Three projects focus on either factors that underlie maternal tobacco use and its effects on neonatal brain development, or on nicotine addiction in mentally ill (e.g., schizophrenic) patients. Finally, one project is examining archived tobacco industry documents to determine whether the industry has directly engaged in the use of third parties to influence tobacco control policymaking in Colorado.

CTRP's Role in Enhancing Research Capacity within Colorado

As detailed in the 2003 Call for Applications (*Attachment 1*), the types of research projects CTRP funds include Independent Investigator awards (i.e., Research Projects and Innovative Development and Exploratory Awards (IDEAs)) career development awards (i.e., Postdoctoral Fellowships and Dissertation Research Awards), and participatory research projects (Community-Academic Research Award or CARA). CTRP's Research Priorities support investigations into the etiology, pathogenesis, diagnosis and treatment of tobacco- and addiction-related diseases and the development, implementation, evaluation, and dissemination of existing or novel approaches to tobacco control and substance abuse education.

Investigator-initiated Research
Individual Research Project Awards fund investigator-initiated research projects. The awards typically support research for which there is sound background information and promising supporting data from preliminary studies.

Innovation in Research
Innovative Developmental and Exploratory Awards (IDEAs) fund developmental or exploratory research that is not yet sufficiently mature to compete successfully for an individual research award. Although the proposed research might lack adequate pilot data or proven methods, it is creative, intellectually exciting, and shows clear promise to yield findings that could lead to breakthroughs in the field.

Research Training
CTRP offers three awards types that are aimed at enhancing the scientific infrastructure for tobacco-related research in Colorado. New Investigator Awards are designed to enable young researchers in transition (e.g., postdoctoral researcher to junior faculty) to initiate an independent research program. Postdoctoral Fellowship Awards allow researchers early in their careers to receive training in tobacco- or substance abuse-relevant disciplines. Dissertation Research Awards provide support for the dissertation research of doctoral candidates who wish to pursue research relevant to CTRP goals.

Participatory Research
Jointly funded by the State Tobacco Education and Prevention Partnership (STEPP) and CTRP, CARAs require a collaborative partnership between experienced academic researchers and community based organizations (CBOs), or state or local tobacco prevention and control initiatives to perform scientifically rigorous research into tobacco control issues.

Table 3 details the allocation of funds by award mechanism (i.e., type of grant):

Table 3

Award Distribution – by Type of Award

Type of Award	Awards (% of total)	Amount Funded (%)
Independent Investigator Awards		
Research Projects	18 (44)	$10,126,459 (78)
IDEA Projects	12 (29)	$1,595,087 (12)
Career Development Awards		
New Investigator	3 (7.5)	$751,914 (6)
Postdoctoral Fellowships	3 (7.5)	$265,028 (2)
Dissertation Research Awards	5 (12)	$250,084 (2)
Total	**41 (100)**	**$12,988,572 (100)**

Stated another way, about half of CTRP's ongoing grants are Research Projects, which have been evaluated by peer reviewers as having sufficient significance for the field(s), suitable approaches for the proposed research, and substantial feasibility to accomplish the desired results. Since Research Projects require more resources (e.g., supported staff, supplies, equipment) relative to other award mechanisms, most of our current funding supports these endeavors. Conversely, IDEA projects are considered to be "high risk" with respect to feasibility, but should they be successful, they could advance our understanding of tobacco-related research significantly. Finally, about one-quarter of current CTRP projects are supporting the career development of young investigators who have demonstrated a commitment to pursuing research relevant to the goals of CTRP. Community-Academic Research Awards (CARAs) were offered for the first time in FY 2003 but none of the submitted applications received funding, reflecting a need for CTRP to better define the targeted research and evaluation criteria for this mechanism.

(c) Other Funding: State and Federal Funding for Tobacco- and Substance-Abuse-Related Research

Included in the required Annual Progress Reports submitted by all funded investigators, all other support from both federal and state sources for tobacco- or substance abuse-related research projects are itemized. These additional funds may have been procured by CTRP-supported investigators either prior to or subsequent to receipt of CTRP monies. The total amount of other funding for research relevant to the mission of CTRP, distinct from work supported by CTRP funds, is provided below in aggregate form:

Federal: $13,219,002
Other State: $0

Though not specified by SB 00-071 reporting requirements, investigators receiving support from CTRP may be requested to report future extramural funding received either in complement to or as a result of prior CTRP support. As part of the Program's mission to enhance Colorado's capacity for tobacco- and substance abuse-related research, it is our aim to track how CTRP funding may facilitate the efforts of Colorado investigators to increase federal and state support for their research.

(d) Relationship Between Each Project and the Overall Strategy of the Colorado Tobacco Research Program

The relationship between funded research and the overall strategy of CTRP is determined by assessing the relevance of each project to tobacco use, substance abuse, and/or tobacco-related disease. Following the receipt of grant applications, and prior to the peer review process, all applications are screened for their direct relevance to tobacco or substance use or tobacco-related disease. Briefly, most of the proposals reviewed in the tobacco prevention, cessation, policy and epidemiological disciplines focus directly on human tobacco use and/or tobacco control issues, making their relevance to CTRP's mission apparent. Those applications that directly focus on the etiology, pathology, diagnosis or treatment of a specific tobacco-related disease, for which there is unequivocal epidemiological evidence, are also considered highly relevant to CTRP's mission. In contrast, those research proposals focused on basic biological phenomena must demonstrate how the research will yield insights into tobacco-specific health effects. Only those applications considered relevant to the goals of CTRP are forwarded for scientific peer review by an appropriate review panel or "study section".

Research funded by CTRP should provide novel methods for tobacco use prevention or address the needs of current and/or former smokers. To this end, CTRP supports tobacco-related research in biomedical science, neuroscience, social and behavioral science, epidemiology, public health, policy and economic analysis. CTRP invites investigations into the etiology, pathogenesis, diagnosis and treatment of tobacco-related diseases and the development, implementation, evaluation, and dissemination of existing or novel approaches to tobacco control and tobacco education. CTRP will consider for funding all proposals that meet the relevance criteria. However, we especially encourage applications that address the following topics identified as high priority by CTRP. *For examples of research funded by CTRP in the past, please visit our website at www.cu.edu/ctrp.*

2003 CTRP Research Priorities

- Research that addresses specific Colorado needs with regard to tobacco control among underserved and/or vulnerable populations in all areas of investigation.
- Studies examining all aspects of secondhand smoke exposure.
- Racial, ethnic, age and/or gender-based differences in tobacco interventions and in smoking-related diseases.

- Biomedical research that addresses the health needs of current and/or former smokers, especially translational and clinical studies to develop and validate novel treatments, prevention strategies, validation of early diagnostics, as well as development of more relevant animal models for tobacco-related diseases or addiction.
- Research focused on tobacco-related heart disease, lung illnesses and/or cancers.
- Research focused on prevention of tobacco use across the tobacco control continuum, especially studies of environmental factors that influence initiation of tobacco use, including the role of the tobacco industry.
- Research on tobacco, alternative tobacco / nicotine delivery devices, and tobacco smoke constituents in addition to nicotine that contribute to tobacco-related diseases and to addiction as well as potentially reinforcing the actions of nicotine.
- Evaluative research that focuses on the impact of state and local public policies and programs, particularly among specific populations.
- Studies that use Colorado's data collections (e.g., 2002 Tobacco Attitudinal Baseline Survey) for secondary data analysis.

2001 Funding Cycle

As part of its first cycle of funding, CTRP was legislatively mandated to support a baseline evaluation survey to gather information about tobacco-related behavior and attitudes of children and adults in Colorado. A separate Request for Proposals for this contract was issued; following a review of submitted proposals by the CTRP Scientific Advisory Committee, the $1.5 million contract for the Tobacco Attitudinal Baseline Survey (TABS) was granted to Arnold Levinson, Ph.D., of AMC Cancer Research Center. Results from the TABS were presented in the FY 2002 Annual Report and are available online at www.cdphe.state.co.us/cohid/tabsdata.html.

In response to the 2001 Call for Applications, CTRP awarded a total of $4.64 million for 14 grants to individual investigators at 6 research organizations. This funding level represents a "payline" of 23% of all applications submitted during our first funding cycle.

Research Projects initiated in FY 2001 receiving support from CTRP in FY 2003

(grouped within funding cycles and by research discipline)

Disease Diagnosis & Treatment

1. **Telomerase Expression in Tobacco Associated Oral Cancer, Award #1R-013, *Research Grant*, $718,007 *(Direct: $494,530; Indirect: $223,477)*** - Evaluates a host of tobacco associated pre-cancerous and cancerous oral lesions in order to assess potential malignant risk. Principal Investigator - Robert O. Greer, D.D.S., Professor and Chair, Department of Diagnostic and Biological Sciences and Professor of Pathology and Medicine, University of Colorado Health Sciences Center. Start date 7/1/2001; end date 6/30/2004.

2. **Epithelial Injury by Cigarette Smoke: Sulfur Metabolism, Award #1D-065, *Dissertation Grant*, $59,928 *(Direct: $59,928)*** - Examines how smoking may affect the DNA of lung cells so as to predispose a person to lung cancer and possibly cause depletion of vital nutrients to lung cells. Principal Investigator – Michail I. Panagiotidis, M.S., graduate student at National Jewish Medical & Research Center. Mentor - Carl W. White, M.D., Senior Faculty Member, National Jewish Medical & Research Center, and Professor of Pediatrics at the University of Colorado Health Sciences Center. Start date 7/1/2001; end date 9/30/2003.

3. **CO_2–Assisted Nebulization for Drugs for Lung Ailments, Award #1R-031, *Research Grant*, $733,539 *(Direct: $524,752; Indirect: $208,787)*** - Focuses on two major tobacco-related diseases, lung cancer and emphysema, and provides guidelines that allow formulations of new treatment compounds to be delivered into the lungs. Principal Investigator - Robert E. Sievers, Ph.D., Professor, Department of Chemistry and Biochemistry, University of Colorado at Boulder. Start date 7/1/2001; end date 6/30/2004.

4. **Inflammation, Oxidative Stress and Dysphasia in COPD, Award #1R-032, *Research Grant*, $248,843 *(Direct: $173,879; Indirect: $74,964)*** - Identifies subjects at high risk for lung cancer by examining phlegm for pre-malignant and malignant cells. Principal Investigator - Philip E. Silkoff, M.D., Assistant Faculty Member, Department of Medicine, National Jewish Medical & Research Center. Start date 7/1/2001; end date 6/30/2003.

Prevention & Cessation

1. **Colorado Anti-Tobacco PSA Message Sensation Value Project, Award #1R-014A, *Research Grant*, $568,320 – *(Direct: $363,026; Indirect: $205,294)*** - Tests the effectiveness of a brief media-based tobacco prevention program on producing changes in adolescents' attitudes toward smoking. Principal Investigator - Donald W. Helme, Jr., Ph.D., Assistant Scientist, Cooper Institute, Denver. Start date 7/1/2001; end date 6/30/2004.

2. **ETS Reduction Counseling for Families of Asthmatic Children, Award #1R-018, *Research Grant*, $795,859 *(Direct: $524,944; Indirect: $270,915)*** - Implements an environmental tobacco smoke reduction program with the families of inner city asthmatic children. Principal Investigator - Mary Dorothy Klinnert, Ph.D., Assistant Professor, Department of Pediatrics, National Jewish Medical & Research Center. Start date 7/1/2001; end date 6/30/2004.

3. **Prediction of Tobacco-Using Groups in Pre-Adolescent Youth, Award #1R-033, *Research Grant*, $671,861 *(Direct: $480,244; Indirect: $191,617)*** – Facilitates the determining of how prevention programs should be developed, and will have important implications for the design of culturally appropriate prevention programs. Principal Investigator - Randall C. Swaim, Ph.D., Research Scientist, Psychology, Colorado State University. Start date 7/1/2001; end date 6/30/2004.

4. **Household Factors and Passive Smoke Exposure of Preschool Children, Award #1D-068, *Dissertation Grant*, $44,766 *(Direct: $44,766)*** - Explores the factors that families identify as being important in developing rules about smoking in their homes and cars. Principal Investigator - Yvonne Kay Yousey, Doctoral Candidate, University of Colorado at Denver, MS, CPNP, Senior Instructor, School of Nursing, University of Colorado Health Sciences Center. Mentor - Kitty Corbett, Ph.D., MPH, Associate Professor, Health & Behavioral Sciences, Anthropology, University of Colorado at Denver. Start date 7/1/2001; end date 9/30/2003.

PROJECTS INITIATED IN 2001 AND COMPLETED IN FY 2003

Disease Diagnosis & Treatment

1. **Study of the Effect of the Tobacco Carcinogen Benzo(a)pyrene in *Saccharmyces cerevisiae*, Award #1I-044, *IDEA Grant*, $113,250 *(Direct: $74,515; Indirect: $38,735)*** - This study used budding yeast as an experimental model to investigate the consequences of exposure to the major carcinogen in tobacco, benzo(a)pyrene. This will help our understanding of similar processes in human cells and aims to contribute to the discovery and design of the drugs for tobacco-related diseases including lung cancer. Principal Investigator - Mingxia Huang, Ph.D., Assistant Professor, Department of Biochemistry and Molecular Genetics, University of Colorado Health Sciences Center. Start date 7/1/2001; end date 12/31/2002.

Mental Health

1. **Tobacco and Schizophrenia Affect Prenatal Brain Development, Award #1I-051, *IDEA Grant*, $113,250 *(Direct: $75,000; Indirect: 38,250)*** – Focused on increasing our understanding of both the negative health effects of tobacco on early brain development and on the genetically-mediated prenatal brain development in those most at risk for later tobacco use. Principal Investigator - Randal G. Ross, M.D., Associate Professor, Department of Psychiatry, University of Colorado Health Sciences Center. Start date 7/1/2001; end date 3/31/2003.

Nicotine Addiction

1. **Chronic Nicotine Effects in Mouse Hippocampal CA3 Region, Award #1F-059, *Postdoctoral Fellowship*, $86,400 *(Direct: $80,000; Indirect: $6,400)*** - Investigated chronic nicotine effects in the CA3 region of the hippocampus from inbred mice. Principal Investigator - Peter Dobelis, Ph.D., Post Doctoral Fellow, Pharmacology, University of Colorado Health Sciences Center. Research Advisor – Kevin Staley, M.D., Associate Professor, Neurology, University of Colorado Health Sciences Center. Start date 7/1/2001; end date 6/30/2003.

Prevention & Cessation

1. **Tobacco Use by Foster Care Youth and Professional Responses, Award #1I-054, *IDEA Grant*, $104,866 *(Direct: $74,958; Indirect: $29,908)* -** This study examined the role of tobacco use among foster children and youth, aged 10-17, and how a respondent group of professional workers and foster parents help these foster children with smoking cessation and smoking prevention. Principal Investigator - Mona C. Struhsaker Schatz, D.S.W., Professor, Department of Social Work, Director, Education and Research Institute for Fostering Families, Colorado State University. Start date 7/1/2001; end date 6/30/2003

2002 Funding Cycle

In 2002, CTRP awarded a total of $6.57 million for 16 grants to individual investigators at 5 research organizations. This funding level represents a "payline" of 33% of all applications submitted that year.

2002 Research Projects receiving support from CTRP in FY 2003

Disease Diagnosis & Treatment

1. **Silibinin Treatment of Bladder Cancer, Award #2R-008, *Research Grant,* $713,751 – *(Direct: $467,188; Indirect: $246,563)*** - Will determine the efficacy of a natural compound (currently being tested for treatment of prostate cancer) in combating bladder cancer. Principal Investigator - Michael L. Glode, M.D., Professor of Medicine, Division of Medical Oncology, University of Colorado Health Sciences Center. Start date 7/1/2002; end date 6/30/2005.

2. **Tobacco and Gene Expression, Award #2I-012, *IDEA Grant,* $103,178 – *(Direct: $75,000; Indirect: $28,178)*** – Seeks to identify heretofore unknown tobacco-sensitive genes so as to permit assessment of their relevance to tobacco-related disease. Principal Investigator: William H. Hanneman, Ph.D., Assistant Professor, Environmental Health Department, Colorado State University. Start date 7/1/2002; end date 12/31/2003.

3. **Regulation of Tumor Suppression by TGF-beta in Lung Cancer, Award #2R-045, *Research Grant,* $608,310 – *(Direct: $423,572; Indirect: 184,738)*** – Seeks to define the mechanism by which negative growth hormones and tumor suppressors control the proliferation of normal vs. lung cancer cells. Principal Investigator: Xuedong Liu, Ph.D., Assistant Professor, Department of Chemistry and Biochemistry, University of Colorado at Boulder. Start date 7/1/2002; end date 6/30/2005.

4. **Regulation of Cell Division by mMps1/TTK in Lung Cancer, Award #2F-047, *Postdoctoral Fellowship,* $86,400 – *(Direct: $80,000; Indirect: $6,400)*** – Will pursue the connection between key proteins involved in altered cell division and lung cancer. Principal Investigator: Christopher P. Mattison, Ph.D., Research Associate, MCD Biology, University of Colorado at Boulder. Mentor: Mark Winey, Ph.D., Associate Professor, MCD Biology, University of Colorado at Boulder. Start date 7/1/2002; end date 6/30/2004.

5. **Biomarkers of Smoke-Induced Lung Cancer in a Mouse Model, Award #2D-027, *Dissertation Grant,* $48,320 – *(Direct: $48,320)*** – Seeks to determine if a specific protein can be used to detect the presence of lung cancer. Principal Investigator: Katherine A. Peebles, B.Sc., Graduate Student, Department of Pharmaceutical Sciences, University of Colorado Health Sciences Center. Mentor: Alvin Malkinson, Ph.D., Professor, Department of Pharmaceutical Sciences, University of Colorado Health Sciences Center. Start date 7/1/2002; end date 6/30/2004.

6. **Health Effects of ETS in Urban Minority Children with Asthma, Award #2R-020, *Research Grant,* $796,690 – *(Direct: $523,793; Indirect: $272,897)*** – Will characterize how various smoking behaviors determine children's exposure to secondhand smoke and their corresponding severity of asthma and/or decreased lung function. Principal Investigator – Nathan Rabinovitch, M.D., Assistant Professor, Pediatrics, National Jewish Medical and Research Center. Start date 7/1/2002; end date 6/30/2005.

7. **Novel Polymer-Drug Conjugates for COPD Therapies, Award #2I-031, *IDEA Grant,* $113,371 – *(Direct: 74,750; Indirect: $38,621)*** – Seeks to devise new organic molecules to facilitate delivery of drugs used in the treatment of lung diseases caused by tobacco use. Principal Investigator: Jeffrey W. Stansbury, Ph.D., Professor, Restorative Dentistry, University of Colorado Health Sciences Center. Start date 7/1/2002; end date 12/31/2003.

Mental Health

1. **Nicotine Receptor Expression in Mentally Ill Smokers, Award #2R-030, *Research Grant,* $493,073 – *(Direct: $322,891; Indirect: $170,182)*** – Will determine if nicotinic receptor presence and function are altered in mentally ill patients and how this may contribute to the high prevalence of tobacco addiction in this population. Principal Investigator – Sherry S. Leonard, Ph.D., Associate Professor, Psychiatry Department, School of Medicine, University of Colorado Health Sciences Center. Start date 7/1/2002; end date 6/30/2005.

Nicotine Addiction

1. **Alpha-7 Nicotinic Receptor Role in Hippocampal Development, Award #2R-029, *Research Grant,* $364,343 – *(Direct: $294,706; Indirect: $69,637)*** – Seeks to determine which developmental processes in a critical region of the brain are influenced by a key nicotinic receptor and its relationship to tobacco addiction. Principal Investigator – Catherine E. Adams, Ph.D., Assistant Professor, Psychiatry Department, School of Medicine, University of Colorado Health Sciences Center. Start date 7/1/2002; end date 6/30/2005.

2. **Nicotinic Receptor Mediation of Anxiety and Cognition, Award #2R-033, *Research Grant,* $771,750 – *(Direct: $525,000; Indirect: $246,750)*** – Will define factors critical to the transition from tobacco experimentation to addiction by examining the effects of nicotine on emotional calming and its ability to enhance concentration. Principal Investigator – Jeanne M. Wehner, Ph.D., Professor, Institute for Behavioral Genetics, University of Colorado at Boulder. Start date 7/1/2002; end date 6/30/2005.

Prevention & Cessation

1. **Candidate Genes for Tobacco Use and Nicotine Dependence, Award #2I-034, *IDEA Grant,* $110,250 – *(Direct: $75,000; Indirect: $35,250)*** – Seeks to identify presence and role of genes that may influence adolescents' risk for tobacco addiction. Principal Investigator: Marissa A. Ehringer, Ph.D., Postdoctoral Fellow, Institute for Behavioral Genetics, University of Colorado at Boulder. Start date 7/1/2002; end date 12/31/2003.

2. **Tobacco and Alcohol Use in College: A CU Developmental Study, Award #2R-041, *Research Grant,* $691,581 – *(Direct: $470,463; Indirect: $221,118)*** – Seeks to advance our understanding of the personal and social characteristics that influence tobacco and alcohol use among male and female college students. Principal Investigator – Richard Jessor, Ph.D., Professor of Psychology, and Acting Director, Research Program on Health Behavior, Institute of Behavioral Science, University of Colorado at Boulder. Start date 7/1/2002; end date 6/30/2005.

3. **Motivational Orientations and the Smoking Cessation Process, Award #2D-007, *Dissertation Grant,* $48,034 – *(Direct: $48,034)*** – Will examine roles of incentives and rewards in enabling smokers to quit. Principal Investigator: Nicholas E. Perrine, M.S., Graduate Student, Department of Psychology. Mentor: Patricia Aloise-Young, Ph.D., Assistant Professor, Department of Psychology, Colorado State University. Start date 7/1/2002; end date 6/30/2004.

4. **Combined Effects of Alcohol and Nicotine, Award #2D-048, *Dissertation Grant*, $49,036 – *(Direct: $49,036)*** – Will pursue connections between biological and psychological motivations influencing alcohol and tobacco use in humans. Principal Investigator: Annie R. Peters, BS/BA, Graduate Student, Department of Psychology, University of Colorado at Boulder. Mentor: Kent Hutchison, Ph.D., Assistant Professor, Department of Psychology, University of Colorado at Boulder. Start date 7/1/2002; end date 6/30/2004.

5. **MATE: Media and Tobacco Education, Award #2R-021, *Research Grant,* $637,714 – *(Direct: $456,881; Indirect: $180,833)*** – Seeks to develop, evaluate and test the efficacy of a theoretically-based media literacy intervention to help children counter the influence of smoking imagery found in popular culture. Principal Investigator – Barbara J. Walkosz, Ph.D., Assistant Professor, Communication Department, University of Colorado at Denver. Start date 7/1/2002; end date 6/30/2005.

2002 TERMINATED PROJECTS

1. **Zebrafish: A Model for Nicotine Developmental Toxicity, Award #2R-019, *Research Grant,* $772,324 – (*Direct: $515, 529; Indirect: $256,795)*** – Sought to develop an alternate vertebrate research model to define how nicotine modifies central nervous system development and function. Principal Investigator – Robert L. Tanguay, Ph.D., Assistant Professor, School of Pharmacy, University of Colorado Health Sciences Center. Start date 7/1/2002; terminated 2/28/2003 due to Principal Investigator's relocation to Oregon State University.

2003 Funding Cycle

In 2003, CTRP awarded a total of $3 million for 14 grants to individual investigators at 6 research organizations. This funding level represents a "payline" of 40% of all applications submitted that year.

Disease Diagnosis & Treatment

1. **Smoking Cessation, Intramuscular Lipid & Insulin Action, Award #3K-027,** ***New Investigator Award,*** **$291,065 –** ***(Direct: $269,505; Indirect: $21,560)*** - Will investigate possible means to explain smokers' increased risk for cardiovascular disease by examining the correlation between smoking, muscle fat content and response to insulin. Principal Investigator - Bryan Bergman, Ph.D., Postdoctoral Reseacher, Division of Medical Division of Endocrinology, Diabetes, and Metabolism, University of Colorado Health Sciences Center. Start date 7/1/2003; end date 6/30/2006.

2. **Antioxidants and Oxidative Damage in Smokers with COPD, Award #3I-005,** ***IDEA Grant,*** **$140,391 –** ***(Direct: $100,000; Indirect: $40,391)*** – Seeks to define mechanisms for why some smokers are more susceptible to chronic obstructive pulmonary disease. Principal Investigator: Russell P. Bowler, M.D. Ph.D., Assistant Professor, National Jewish Medical and Research Center. Start date 7/1/2002; end date 6/30/2005.

3. **Low Birth Weight: The Interaction of Smoking & Altitude, Award #3I-024,** ***IDEA Grant,*** **$152,310 –** ***(Direct: $99,851; Indirect: $52,459)*** – Will utilize geographical information system analyses to study additive effects of maternal smoking and altitude on low birth weight on child susceptibility to neonatal and juvenile diseases. Principal Investigator: Susan Niermeyer, M.D., Associate Professor of Pediatrics, Section of Neonatology, The Children's Hospital / University of Colorado Health Sciences Center. Start date 7/1/2003; end date 12/31/2004.

4. **Mechanism of Tobacco-Induced Mutations in Lung Cancer, Award #3I-010,** ***IDEA Grant,*** **$152,827 –** ***(Direct: $99,526; Indirect: $53,271)*** – Will explore potential chemotherapeutic strategies for lung cancer by identifying genes involved in the response to mutagenic agents in tobacco smoke. Principal Investigator: Robert A. Sclafani, Ph.D., Professor, Biochemistry and Molecular Genetics Dept., University of Colorado Health Sciences Center. Start date 7/1/2003; end date 6/30/2005.

5. **Antibodies Against Endothelial Cells Cause Emphysema in Rats, Award #3I-013,** ***IDEA Grant,*** **$149,220 –** ***(Direct: $100,000; Indirect: $49,220)*** – Seeks to determine if smokers' susceptibility to emphysema results from injury to the lung's blood vessels as opposed to its surface tissues. Principal Investigator: Laimute Taraseviciene-Stewart, Ph.D., Instructor, Department of Pulmonary Medicine, University of Colorado Health Sciences Center. Start date 7/1/2003; end date 6/30/2005.

6. **Nitropolycyclic Aromatics in Secondhand Tobacco Smoke, Award #3R-011,** ***Research Grant,*** **$366,499 –** ***(Direct: $242,614; Indirect: $123,845)*** – Will employ a sophisticated analytical method to characterize the production of specific tobacco carcinogens in secondhand smoke at higher altitudes. Principal Investigator – Kent J. Voorhees, Ph.D., Professor, Department of Chemistry and Geochemistry, Colorado School of Mines. Start date 7/1/2003; end date 6/30/2005.

7. **Cigarette Smoke, Oxidants, and S-adenosylmethionine, Award #3R-020,** ***Research Grant,*** **$468,262 –** ***(Direct: $310,576; Indirect: $157,686)*** – Seeks to determine if smoker susceptibility to pulmonary disease and cancer is related to the activity of a key antioxidant pathway in the lung. Principal Investigator: Carl W. White, M.D., Professor of Pediatrics, National Jewish Medical and Research Center. Start date 7/1/2003; end date 6/30/2005.

Mental Health

1. **Nicotinic Receptor Subunits Involved in Sensory Inhibition, Award #3R-018, *Research Grant,* $478,097 – *(Direct: $311,450; Indirect: $166,647)*** – Seeks to define the relationship between nicotine activity, schizophrenic psychosis and the associated overwhelmed sensory response using an animal model to study the critical neural components involved. Principal Investigator – Karen E. Stevens, Ph.D., Associate Professor, Department of Psychiatry, School of Medicine, University of Colorado Health Sciences Center. Start date 7/1/2003; end date 6/30/2005.

Nicotine Addiction

1.` **Presynaptic Nicotinic Receptor Subtypes in Dopamine Neurons, Award #3F-034, *Postdoctoral Fellowship,* $92,228 – *(Direct: $85,396; Indirect: $6,832)*** –Will improve our knowledge for designing drugs for smoking cessation by characterizing critical nerve receptors. Principal Investigator – Outi Salminen, Ph.D., Research Associate, Institute for Behavioral Genetics, University of Colorado at Boulder. Mentor: Allan C. Collins, Ph.D., Professor, Institute for Behavioral Genetics, University of Colorado at Boulder. Start date 7/1/2003; end date 6/30/2005.

2. **Immunochemical Protocols for Nicotinic Receptors, Award #3I-030, *IDEA Grant,* $146,565 – *(Direct: $99,699; Indirect: $46,866)*** – Seeks to establish a working set of diagnostic approaches to probe the diversity, composition and properties of brain nicotinic receptors. Principal Investigator – Paul Whiteaker, Ph.D., Research Associate, Institute for Behavioral Genetics, University of Colorado at Boulder. Start date 7/1/2003; end date 6/30/2004.

Prevention & Cessation

1. **A Lifestyle Typology to Model Youth Smoking, Award #3I-002, *IDEA Grant,* $137-449 – *(Direct: $99,963; Indirect: $37,486)*** – Aims to develop a sophisticated marketing approach to identify those youths who are most likely to begin using tobacco. Principal Investigator – Andrew J. Czaplewski, Ph.D., Assistant Professor, Dept. of Marketing, Strategy and International Business, University of Colorado at Colorado Springs. Start date 7/1/2003; end date 6/30/2004.

2. **Smoking Cessation Among American Indian Elders, Award #3K-001, *New Investigator Grant,* $267,925 – *(Direct: $248,078; Indirect: $19,847)*** – Will determine if culturally appropriate, motivational interviewing methods improve smoking cessation treatment compliance within a population that has the highest smoking rates in the nation. Principal Investigator – Patricia Nez Henderson, M.D., Assistant Professor, Department of Psychiatry, University of Colorado Health Sciences Center. Start date 7/1/2003; end date 6/30/2006.

3. **The Effect of Sertraline on Depression in COPD, Award #3K-026, *New Investigator Grant,* $192,924 – *(Direct: $178,633; Indirect: $14,291)*** – Will examine the effectiveness of an antidepressant on improving treatment adherence of patients with smoking-induced lung disease. Principal Investigator: Rachel J. Norwood, M.D., Instructor, Department of Medicine, National Jewish Medical and Research Center. Start date 7/1/2003; end date 6/30/2005.

Policy and Public Health

1. **Tobacco Industry Involvement in Colorado, Award #3I-032, *IDEA Grant,* $58,160 – *(Direct: $58,160)*** – Will examine archived tobacco industry documents to determine whether the industry has directly engaged in the use of third parties to influence tobacco control policymaking in Colorado. Principal Investigator – Anne F. Landman, B.A., Tobacco Document Research Specialist, American Lung Association of Colorado. Start date 7/1/2003; end date 6/30/2004.

(e) Summary of Research Findings

Findings of CTRP studies initiated during the first two funding cycles

For those projects that just begun on July 1, 2003, since awardees are only 4 months into their research projects, no detailed findings for these most recent awards are yet available. The following section summarizes the results of active grants funded in 2001 or 2002. These projects, which have been ongoing for at least one year, are grouped within research areas by principal investigator (in alphabetical order) and the lay abstracts of each project, composed by the investigators themselves, detail the results of their respective projects.

Disease Diagnosis & Treatment

Glode, Michael
Silibinin Treatment of Bladder Cancer
University of Colorado Health Sciences Center

Bladder cancer is the most common type of cancer associated with exposure to chemicals including those found in tobacco smoke. Smokers have a 4-fold higher incidence of bladder cancer compared to nonsmokers, and up to 1/2 of all urinary bladder cancers are related to smoking. Thus, smoking is a significant contributing factor to development of bladder cancer. Standard treatment may include surgery, chemotherapy, radiation therapy, biological therapy, and combinations of these. However, the surgery has undesirable physical and psychological effects; metastases are difficult to treat, and recurrence of primary disease is frequent, leading to tumors with higher metastatic potential. We have an ongoing Phase I/II clinical trial with silibinin to treat hormone refractory and hormone naive prostate cancer patients. This study is based on our focus in defining the mechanism of silibinin, present in milk thistle extract, in controlling the growth of various cancer cells, as well as its cancer preventive and therapeutic efficacy. Here, we proposed studies to establish the efficacy of silibinin in controlling growth of bladder cancer cells.

Aims for the project are to: 1) Examine the growth inhibitory effect of silibinin in established and primary bladder cancer cell lines, and determine its mechanism of action; 2) Examine the anti-tumorigenic effect of silibinin in an animal bladder cancer model; and 3) Measure silibinin levels in urine samples obtained from prostate cancer patients enrolled in our Phase I/II study who are receiving silibinin. During year one of funding, we have nearly completed studies described in aim 1, have initiated studies in aim 3, and are in process of obtaining necessary animal approvals to begin studies described in aim 2. Our observations in human bladder cancer cell lines (aim 1) are are follows: Silibinin inhibits growth, causes cell cycle arrest, and induces apoptosis (programmed cell death) in these cells. Our studies demonstrated mechanisms of action at the cell cycle and cell signaling levels. We initiated studies with primary human bladder cancer cells (derived directly from human tumors), and demonstrated that these cells also show inhibition of cell growth in response to silibinin. Cell cycle and cell signaling studies, along with cytology and chromosomal analysis, are underway in these tumor samples. We have also made progress in studies desribed in aim 3. The original clinical protocol and consent form for the prostate cancer-silibinin study was amended to allow us to collect urine samples at baseline and throughout the study. Institutional Review Board approval was obtained, and we have now collected urine samples at various time points from nine patients enrolled on the study. We are in the process of working out methods to detect various forms of silibinin.

In summary, these preliminary studies support the feasibility of using silibinin to inhibit growth of bladder cancer cells. We will complete the studies in cell lines and primary tumor specimens in year 2. We will then focus on demonstration of silibinin's effect in the bladder cancer animal model, and in analysis of silibinin in urine samples of patients to determine the likelihood of achieving therapeutic dose levels in the bladder.

Greer, Robert O.
Telomerase Expression in Tobacco Associated Oral Cancer
University of Colorado Health Sciences Center

During the second year of this project directed toward evaluating the role of telomerase in tobacco associated oral cancer, we have concentrated on two principal tasks, both designed to address Specific Aims I and II of the project:

1. Procurement of tissue for the head and neck cancer tissue bank from patients with tobacco associated oral cancers and precancers, so that we will be able to evaluate the number of proposed samples stated in the application (N=240).
2. Performing telomerase enzyme extraction on frozen tissues and paired normal tissues from currently banked specimens.

Since the initiation of the project, we have accessioned 77 new cases of oral squamous cell carcinoma and 46 cases of oral epithelial dysplasia. We have begun testing for telomerase expression in these tobacco-associated lesions (Specific Aim I). We have also begun to correlate telomerase expression with the various histologic grades of oral squamous cell carcinoma (Specific Aim II). A total of 27 new oral cancers, demonstrating telomerase overexpression were identified and evaluated in Year 2 of the grant (Specific Aim II).

We will continue to accrue tissue from tobacco associated oral mucosal cancer and oral tissue demonstrating varying degrees of oral precancer during the course of the next eighteen months and continue to (1) test tissue samples for telomerase expression, (2) correlate telomerase expression with the histologic stages of squamous cancers, and (3) attempt to correlate telomerase expression with oral precancerous and cancers to determine if telomerase expression may be a rate limiting step for tumor progression. The impact of these studies should enable us to correlate telomerase expression with risk for malignancy and establish clinical outcome correlations so as to better manage patients.

Hanneman, William
Tobacco and Gene Expression
Colorado State University
[*Principal Investigator had not submitted abstract prior to press deadline*]

Huang, Mingxia
Study of the Effect of the Tobacco Carcinogen Benzo(a)pyrene in *Saccharmyces cerevisiae*
University of Colorado Health Sciences Center

This project was focused on the biological effect of exposure to benzo(a)pyrene, a major carcinogen in the smoke of tobacco, using the budding yeast Saccharomyces cerevisiae as a model system. Benzo(a)pyrene is converted to the ultimate carcinogenic metabolite, benzo(a)pyrene-7,8-diol-epoxide (BPDE) by cytochrome P450 enzymes. In human cells, one of the first steps of metabolism of benzo(a)pyrene to BPDE is the binding of benzo(a)pyrene to the aryl hydrocarbon receptor (AHR) in the cytoplasm. The ligand-bound AHR then translocates to the nucleus and forms a heterodimeric complex with AHR nuclear translocator (ARNT). The AHR/ARNT complex binds to the dioxin responsive elements (DRE) in the promoters of a subset of genes encoding detoxification enzymes, including P450 enzymes CYP1A1 and CYP1A2. CYP1A1 is the major monooxygenase that converts benzo(a)pyrene to BPDE and other metabolites, some of which can generates redox cycling. Redox cycling and increase in cytochrome P450 enzymes leads to the increase of reactive oxygen species (ROS) and oxidative damage inside the cell.

We had originally proposed to reconstitute benzo(a)pyrene-induced transcriptional activation in yeast and use this system to screen for additional factors involved in this process. We have constituted a reporter strain for this purpose and assessed whether this strain is suitable for the proposed genetic screens.

Liu, Xuedong
Regulation of Tumor Supression by TGF-beta in Lung Cancer
University of Colorado at Boulder

The goal of this study is to identify the molecular mechanisms by which TGF-ß down regulate Skp2 expression which results in stabilization of the p27KIP in normal epithelial cells and determine whether these control mechanisms are disrupted during lung carcinogenesis.

In the first year of this project, we have demonstrated that TGF-ß treatment leads to stabilization of p27Kip1 during G1 to S transition. We found that TGF-ß negatively regulates components of the SCF complex, which degrades the p27Kip1 during the G1 to S transition, through two distinct mechanisms. Using a pulse-chase analysis, we demonstrated that the stability of Skp2 decreases in the presence of TGF-ß. Destabilization of Skp2 by ubiquitin-mediated proteolysis was also demonstrated that in an in vitro degradation system using cell extracts prepared from TGF-ß treated cultured cells. In addition, TGF-ß treatment decreases the levels of Cks1 mRNA. The

deficiency of Cks1 in TGF-ß-treated cells likely contributes to stabilization of p27Kip1 and destabilization of Skp2, because in the absence of Cks1, SCFSkp2 cannot ubiquitylate p27Kip1; instead, self-ubiquitination of Skp2 ensues. Thus, stabilization of the cell cycle inhibitor p27Kip1 and cell growth inhibition in response to TGF-ß occur in part through limiting the threshold of the SCFSkp2 ubiquitin ligase by transcriptional and posttranscriptional mechanisms. Proteolysis of cyclin dependent kinase inhibitor p27 occurs predominately in the late G1 phase of the cell cycle through a ubiquitin-mediated protein degradation pathway. Ubiquitination of p27 requires the SCFSkp2 ubiquitin ligase and Skp2 F-box binding protein Cks1. The mechanisms by which Skp2 recognizes Cks1 to ubiquitylate p27 remain obscure. Here we show that Asp 331 in the carboxyl terminus of Skp2 is required for its association with Cks1 and ubiquitination of p27. Mutation of Asp 331 to Ala disrupts the interaction between Skp2 and Cks1. While Asp331 mutation negates the SCF complex's ability to ubiquitylate p27, such a mutation has no effect on Skp2 self-ubiquitination. A conservative change from Asp to Glu at position 331 of Skp2 does not affect Skp2-Cks1 interaction. Our results revealed a unique requirement for a negatively charged residue in the carboxyl terminal region of Skp2 in recognition of Cks1 and ubiquitination of p27. We have already published one paper in Journal of Biological Chemistry and another manuscript has been submitted to Oncogene. Aim1 and 2 of the proposed studies have been completed. We are moving forward with Aim 3 and 4. During our study of Aim 1, we discovered a new avenue for control p27Kip1 degradation, i.e. the involvement of Cks1 in p27 degradation.

Identification and characterization of amino acid residues in Skp2 that are required for association with Cks1 and ubiquitination of p27. Our preliminary data suggest that there are two discrete regions of Skp2 are involved in binding to Cks1. We have identified a negatively charged amino acid Asp331 mapped on the surface of Skp2 structure is required for association with Cks1 and p27 ubiquitination. In addition, our deletion analysis indicates that a twelve amino acid stretch near the carboxyl terminal region of Skp2 is also involved. An alanine scan mutagenesis will be performed to evaluate each of the twelve amino acid residue in carboxyl terminal of Skp2 for their involvement in Cks1 binding. Surface exposed hydrophobic amino acid residue near Asp331 will also be systematically mutated to alanines to elucidate amino acid residues that might provide the main source of binding energy.

2. Determine the molecular mechanism by which Cks1 stimulates ubiquitination of phosphorylated p27 by SCFSkp2. Preliminary studies suggest that Cks1 is required for p27 recruitment and binding to SCFSkp2 complex. Neither Cks1 or SCFSkp2 alone bind phosphorylated p27. We will identify the amino acid residues in Skp2 and Cks1 that are responsible for substrate recognition. In addition, we will test a hypothesis whether Cks1 binding unmask the phosphorylated p27 binding site in Skp2.

3. Determine whether activation of Ras oncogene abrogate Skp2 regulation by TGF-ß. Activating mutations of the K-ras oncogene are found in one-quarter to one-half of human lung adenocarcinomas. We have previously shown that Ras activation abrogates TGF-ß growth inhibition. We will determine whether activation of Ras oncogene disrupt TGF-ß downregulation of Skp2 and promote cell cycle progression.

4. Determine whether decrease in Skp2 expression in lung cancer cells results in accumulation of p27 and restore the growth inhibitory response to TGF-ß. We will use RNAi or antisense approach to reduce the mRNA of Skp2 in lung cancer cells and test the role of Skp2 in tumor aggressiveness.The proposed studies are significant for several reasons. Timed destruction of cell cycle inhibitors such as p27 by the ubiquitin-proteasome pathway plays a critical role in ensuring normal cellular processes. Aberrant degradation of p27 is one of the most common cellular events in the pathogenesis of numerous types of human cancers. The levels of p27 expression in cancer cells have proved to be a powerful prognostic indictor for tumor progression and patient survival. Understanding how normal cells regulate proper levels of p27 and the mechanism of abnormally low levels of p27 in tumor cells will reveal potential targets for therapeutic intervention. Increasing p27 expression in tumor cells by interfering Skp2-Cks1 interaction could prove to be an effective way to control tumor cell proliferation and cancer progression. Resistance to TGF-ß growth inhibition is a hallmark of many tumor cells. Stabilization of p27 by TGF-ß through down regulation of Skp2 may be one of the key mechanisms underlying tumor suppression by TGF-ß. Disruption of TGF-ß signaling may account for overexpression of Skp2 in tumor cells and low levels of p27 that have been observed in many aggressive tumors. Understanding how normal cells maintain proper levels of Skp2 will reveal potential targets for therapeutic intervention. Restoration of TGF-ß regulation of Skp2 or a small molecule inhibitor that can mimic TGF-ß action may be able to increase the abundance of p27 and hence may prove to be valuable for cancer therapy.

Mattison, Christopher
Regulation of Cell Division by mMps1/TTK in Lung Cancer
University of Colorado at Boulder

Every time a cell divides it must equally partition exactly one copy of its DNA to each cell. Defective partitioning of DNA during cell division is strongly correlated with the development of several types of human cancers, including lung cancer. Therefore, investigating the mechanism by which cells ensure proper distribution of DNA during each round of cell division will help us to better understand how cancer arises. The cellular structure that is used to distribute DNA to each cell during division is termed the mitotic spindle. Proper formation of the mitotic spindle and equal distribution of DNA requires the duplication and assembly of centrosomes. Centrosomes, like DNA, must be duplicated once and only once per cell division, and are composed of a number of proteins. The duplicated centrosomes function as the anchor points for pulling each copy of DNA apart during cell division so that each cell gets exactly one copy. Centrosome defects likely lead to uneven DNA distribution to dividing cells. Lung cancers commonly have defects in the number and structure of their centrosomes. The Mps1 protein, discovered in the Winey lab, functions to regulate centrosome duplication. The Winey group has identified an important regulatory event that controls the level of the human Mps1 (hMps1) protein at a critical time when cells duplicate theircentrosomes. The link between centrosome defects and lung cancer makes hMps1 an attractive candidate for study.I have been investigating hMps1 function in centrosome duplication and determine if it has a role lung cancer. One goal of this proposal was to understand how hMps1 is regulated and if that regulation is altered in lung cancers. Technical limitations have lead me to make a new tool, an antibody, for the analysis of hMps1 regulation in cells. Preliminary results indicate the new antibody is working better at recognizing hMps1. In addition, I am in the process of identifying proteins that interact with hMps1, and currently I have isolated at least one exciting candidate protein. This analysis will help us understand what other proteins hMps1 functions with to control centrosome duplication. I also planned to identify the parts of hMps1 important for localization and regulation within the cell. My data indicates that the first 306 amino acids (of 857 total) are necessary and sufficient for mMps1 centrosome localization. Further, work from another scientist in the Winey lab indicates that 110 amino acids in the middle of hMps1 are required to target hMps1 for proper regulation. These results attain the goal for this second aim. I have continued with a more careful analysis of hMps1 using a more sophisticated method in order to better understand how the hMps1 protein regulates itself. This analysis has begun to yield a great deal of exciting data, and I am in the process of determining its impact on hMps1 funciton. Improper hMps1 regulation is likely to cause centrosome defects and may play an important role in the onset or progression of lung cancer. The data presented here gives us some hints as to how the hMps1 protein is regulated. Continuation of the experimentation described above followed by careful analysis will allow a more thorough understanding of how hMps1 functions to control centrosome duplication and ensure proper distribution of DNA.

Panagiotidis, Michail
Epithelial Injury by Cigarette Smoke: Sulfur Metabolism
University of Colorado Health Sciences Center

Tobacco smoke may have profound effects on sulfur-containing amino acids and antioxidants, in the lung and in the body, primarily through its content of a large number of toxic chemicals called “free radicals”. These chemicals are capable of depleting amino acids and antioxidants and can contribute to the pathology of a variety of lung (chronic bronchitis, emphysema) and cardiovascular (heart attack, stroke) diseases. Our laboratory is interested in changes associated with the two important and related biochemical pathways – one that produces cysteine (transsulfuration) used for synthesis of the critical antioxidant glutathione, and the other (transmethylation) that produces S-adenosyl methionine (SAM), the essential methyl donor needed for producing a variety of cell constituents.

As the first part of our proposed study, we developed experimental protocols and conditions required for measuring: 1) levels of SAM and all intermediate metabolites used to produce glutathione, 2) activity levels of enzymes involved in this crucial metabolic pathway and 3) levels of global and site-specific (CpG island) DNA methylation. Specifically, human lung adenocarcinoma cells (A549) were exposed to various free radical-generating systems at different concentrations and time intervals, and changes in sulfur-containing molecules were quantified. Our findings indicate that preservation of SAM, SAH (S-adenosyl homocysteine) (another metabolite in this pathway), and their ratio (SAM / SAH) continues until oxidative stress is profound. Such preservation was associated with elevation of all intermediate metabolites (homocysteine, cystathionine and cysteine) used for increased synthesis of glutathione.

During the second part of our proposed study, we established a model for exposure of cells to cigarette smoke. Briefly, A549 cells were exposed to different concentrations (2.5%, 5%, 10%, 25%, 50% and 100%) of cigarette

smoke extract (CSE) at different time intervals (24 and 48h). Transmethylation and transsulfuration were determined by quantifying changes in the levels of their intermediates. Our findings indicate: 1) absence of cytotoxicity up to 72h of exposure to various concentrations of CSE, 2) increased utilization of both pathways (at 24 and 48h), associated with a decrease in levels of all metabolites, used for increased consumption of glutathione, 3) elevation of SAM and consequently the SAM / SAH ratio (at 48h) suggesting a higher methylation potential and 4) increased levels of DNA damage (at 24 and 48h) after exposure to 100% CSE only.

Currently, experiments in our laboratory are in progress to establish the same experimental protocols and conditions to human primary pharyngeal cells. In addition, we are committed in identifying potential methylation targets that may play a role in the ability of cells to adapt after exposure to CSE.

Peebles, Katherine

Biomarkers of Smoke-Induced Lung Cancer in a Mouse Model

University of Colorado Health and Sciences Center

Lung cancer is the second leading cause of death in the United States. Most people diagnosed with this disease will die from it within 5 years. This is because lung cancer is detected at very late stages, when it is difficult to treat because the cancer has spread from the lung to different parts of the body. Cancer researchers would like to discover a method to detect lung cancer much earlier than they can now, such that the tumor only exists in a relatively small portion of the lung. Tumors like these can be surgically removed, and patient survival would increase dramatically. One method for detecting cancer is to look for biomarkers, proteins that are not found in healthy tissue. The protein heterogeneous nuclear ribonucleoprotein A2/B1 (A2/B1) has been investigated in the clinic as a biomarker for lung cancer. My research aims are to determine how and when this protein is increased during cancer development, so that we can clearly understand its usefulness as a biomarker, and possibly find different targets for novel drug development. In the first year of this project, I have determined that A2/B1 is expressed at intermediate and late stages of tumor growth, and therefore could be useful as a biomarker for lung cancer. This protein also appears to be important for the activation of macrophages, immune system cells. I have also determined that the expression of this gene is not regulated at the point of transcription, the intermediate stage between a gene and it's product. In the next year of my funding I will begin to determine the role of A2/B1 in macrophage activation, and I will further clarify the mechanisms by which it is increased during lung cancer development.

Rabinovitch, Nathan

Health Effects of ETS in Urban Minority Children with Asthma

National Jewish Medical and Research Center

One of the major triggers for asthma in children is exposure to environmental tobacco smoke. Because nicotine-containing products are addictive, parents have difficulty with smoking cessation and try alternative strategies. These include smoking when the child is not home, smoking outdoors, and decreasing the number of cigarettes smoked per day. However, it is unclear whether any of these intermediate strategies truly have benefit and result in decreasing a child's asthma symptoms. A primary objective of this study was to characterize how various smoking behaviors affect tobacco smoke exposure levels and to quantify the dose-response relationship between tobacco smoke exposure and markers of asthma severity such as increased lung inflammation and decreased lung function. Additionally, our intention was to assess whether implementation of environmental measures to reduce tobacco levels will decrease the frequency of exacerbations and reverse the known effects of tobacco smoke on asthma severity over the short and long-term.

In the first year of the study, 50 school-age children with asthma have been recruited into the cohort: 2/3 of whom are exposed to environmental tobacco smoke. Precise measurements of exposure have been performed utilizing portable monitors of tobacco smoke particulate while parents have reported smoking behavior on a daily basis. Concurrent measurements of asthma severity and lung inflammation have been collected and an environmental intervention program designed to decrease smoking exposure has been initiated.

As we begin to analyze our data in the coming year, we will correlate smoking behavior to subsequent smoking exposure and quantify the relationship between different smoking exposures and the severity of asthma in children. This linking of smoking behavior to resultant exposure and finally to asthma severity will be extremely important in defining what recommendations are most effective in decreasing the harmful effects of tobacco smoke on children with asthma.

Sievers, Robert E.

CO_2-Assisted Nebulization for Drugs for Lung Ailments

University of Colorado at Boulder

In this second year, significant research progress has been made. The research results have been published in four journal articles and ten scientific meeting abstracts.

The goals of the second year project were to:

1. Generate fine powder low molecular weight drugs using CAN-BD process
2. Perform parametric studies
3. Perform stability and activity studies

Many small molecular weight drugs, antibiotics and antibodies have successfully been micronized by CAN-BD to the particle size range optimal for pulmonary drug delivery. Parametric studies have been conducted, and the conclusions are that particles generated by CAN-BD are smaller when the solute concentration is lower and the flow ratio of CO2 to liquid solution is increased. A mid-size scaled-up CAN-BD unit (MBD) has been constructed to test the feasibility of nebulizing a larger quantity of model solution (NaCl aqueous solution). We have demonstrated that the unit can micronize NaCl at a rate of 2 grams per minute. Activities of CAN-BD treated anti-CD4 and alpha-1-antitrypsin (AAT, potentially useful for treating emphysema), have been determined. The results indicate that CAN-BD processing of the proteins has virtually no effect on enzymatic activities.

A new application of the CAN-BD process has been developed. We have demonstrated that the fine drug particles (e.g., a water-soluble model like NaCl) can be coated with a biodegradable polymer (e.g., PLGA). This will allow better control of the drug-release profile form the coated particles. The particles are in the size range of 1 to 4 μm, which is adequate for pulmonary delivery.

In addition, a patent application was filed in April 2003, describing a more versatile mixing chamber (a cross) than the tee. In the cross, three fluid streams can be intimately mixed, prior to nebulization. In a tee only two streams can be mixed, while in the cross it becomes easier to synthesize more complex mixtures of pharmaceuticals, stabilizers, surfactants, polymers and excipients, each with solubility limitations in the solvent(s) available. .

The focus of the future work will be to increase the production capacity of the MBD unit, and to improve the coating technology further.

Silkoff, Philip E.

Inflammation, Oxidative Stress and Dysphasia in COPD

National Jewish Medical and Research Center

This project recruited subjects from the Clinical Research Unit's patient database. This study looks at the degree of airway inflammation, oxidative stress (chemicals in the breath which cause damage to the lung tissue) and the amount and type of bacteria, which are colonizing the airways (usually there are few bacteria on healthy lungs). We are trying to see if the degree of inflammation, oxidative species and bacterial colonization will be associated with the severity of the pre-malignant or malignant changes in the lungs.

IRB approval at National Jewish was obtained for this study on August 28th 2001. Currently, approval to recruit patients with severe dysplasia from the University Hospital SPORE program has been requested from both IRB committees. A letter has been submitted to the COMIRB for distribution to patients who have severe and moderate dysplasia. To date, 64 subjects have been screened and 36 subjects have been completed while 6 are active, The results of the premalignant test in sputum has shown 14 normal, 14 mild dysplasia, 8 moderate dysplasia, and 3 severe dysplasia. An interim description of the data so far was presented in June 2003 at the Aspen Lung conference.

Stansbury, Jeffrey

Novel Polymer-Drug Conjugates for COPD Therapies

University of Colorado Health and Sciences Center

Chronic obstructive pulmonary disease (COPD) has a high incidence rate among smokers and is difficult to treat since the ongoing nature of the symptoms requires continual administration of drug compounds designed to help open the airways and treat the problems associated with inflammation in the lungs. The drugs involved are not well tolerated throughout the body as is the case when the drug is taken in pill form. Targeted delivery of the drug to the lungs through inhalation therapy has proven more successful, but a controlled slow release of the drug would be preferred.

The goal of this project is to demonstrate the potential use of novel degradable polymers that either chemically attach or physically entrap suitable bioactive compounds for controlled pulmonary release. Since the polymer-drug combination is intended to be delivered as an aqueous aerosol, this requires that the polymer be stable and not release the drug until it is delivered into the lungs. Once there, the drug release profile and polymer degradation should be predictable and controllable.

During this first year of the project, significant progress has been made in the development of a suitable degradable polymer that appears to meet the stringent demands associated with the use of this material as a carrier for the drugs. A pH-responsive copolymer has been developed that allows the polymer to be stored under dilute acidic aqueous conditions for extended intervals (up to several months) in a collapsed state that avoids swelling and the onset of the degradation process. When the pH is raised, as when introduced into the neutral pH conditions in the lungs, the polymer begins to swell and degrade from an insoluble three-dimensional network to soluble linear chains. As the swelling and degradation occurs, it is expected that any bound or entrapped drug will be released and that the release profile can be controllably governed by combination of swelling and degradation rates of the polymer. We have demonstrated that we can rationally design the polymer structure, based on the co-monomers used and the polymerizations conditions used, to predictably modify the swelling and degradation behavior of the polymers.

The polymeric materials made to this point have been large planar films and disc-shaped specimens that have allowed simple characterization of the swelling and degradation of the various polymer compositions. The next stage of the polymer development will be to prepare the polymers as micro-sized particles. This change should be readily accomplished by using a slightly different polymerization process and the higher surface area associated with the small particles is expected to increase the swelling and degradation rates. The drugs will be incorporated into the polymers during their polymerization and the drug release profiles will be adjusted by further modifications as needed to the polymer composition.

Mental Health

Leonard, Sherry

Nicotine Receptor Expression in Mentally III Smokers

University of Colorado Health and Sciences Center

The prevalence of smoking in the mentally ill is very high (50%), but is inordinately high in schizophrenia. (90%)! Nicotine binds directly to nicotinic receptors on the cell surface in both the brain and periphery. We have shown that nicotinic receptor numbers are increased in smokers and levels are correlated with the number of cigarettes smoked per day. When a person quits smoking, their receptor numbers decline. A growing body of evidence suggests that nicotinic receptor levels are different in multiple brain regions of subjects with schizophrenia, and further that smoking may not regulate them in the same manner as in normal subjects. Nicotinic receptors are formed from five protein subunits, which make a channel that lets the calcium into the cell. There are 11 different genes for nicotinic receptor subunits and the working receptor is formed from different combinations of 5 of these subunits. This proposal studies the expression of individual nicotinic receptor subunits that make up the receptor in postmortem brain of normal smokers and non-smokers and in schizophrenic and bipolar smokers and non-smokers.. Our Specific Aims are addressing the following questions: 1) What are the effects of smoking on nicotinic receptor subunit protein expression in postmortem brain of individuals with no history of mental illness? Progress reported includes the quantification of messenger RNA for the a7 nicotinic receptor subunit in control smokers and non-smokers. We found no change in mRNA for this subunit in control smokers. We also compared expression for 12,000 genes in smokers and non-smokers using a silicon-chip microarray technology in the laboratory. We found that expression of 132 genes was changed in human brain by smoking, including genes in an important excitatory pathway. 2) What are the effects of smoking on nicotinic receptor subunit protein expression in postmortem brain of individuals with schizophrenia and bipolar disorder? Progress reported includes the quantification and comparison of postmortem brain mRNA for the a7 nicotinic receptor subunit between schizophrenic and control smokers and non-smokers. Our findings show that schizophrenics have reduced levels of a7 mRNA and that this is up regulated in schizophrenic smokers. This is consistent with a study published in 2002 showing mutations in the promoter region of the a7 gene. The promoter regulates the amount of expression from the gene. Microarray studies, described above, show that >50 genes are differentially regulated in postmortem brain of schizophrenic subjects compared to controls. 3) Are receptor subunit levels regulated coordinately in human brain? We have completed data on quantification of total

nicotinic receptors on white blood cells from controls and schizophrenics. Collection of blood cells from bipolar subjects is in progress. Total levels of nicotinic receptors will be compared between all three groups.

Ross, Randal G.
Tobacco and Schizophrenia Affect Prenatal Brain Development
University of Colorado Health Sciences Center

Of all groups studied, cigarette smoking is highest in individuals with severe mental illnesses such as schizophrenia. Not only do over 80% of people with schizophrenia smoke, they smoke "harder" (sucking more nicotine out of a cigarette than other smokers) and have greater difficulty quitting. This very high level of cigarette use is presumed to be secondary to the role of nicotine in the development of the illness. One gene that is likely involved in schizophrenia is a gene that makes a brain receptor responsive to nicotine. People with schizophrenia have many fewer of these nicotinic receptors. One of the reasons people with schizophrenia smoke so much is that they are trying to get a lot of nicotine into their body and highly activate their limited number of receptors. This nicotinic receptor also has effects on how individuals respond to simple sounds, especially the ability to inhibit responding to sounds with no relevant information, and this response can be measured in newborn infants. Prenatal tobacco exposure has direct long-term effects on the ability to inhibit behavior, whether this behavior is measured by parental report, neuropsychological tests, or physiological response to auditory stimulation. The primary goal of this proposal was to develop methodology for interrelating genetic vulnerability to schizophrenia (and smoking) and prenatal exposure to smoke.
As a first step in this process, we have explored methodology for examining inhibitory processes in infants. We were most interested in those processes known to be abnormal with genetic risk for schizophrenia. One success to date has focused on a brain response to sound, known as P50 sensory gating. This funding supported findings that infants develop the ability to inhibit brain response to repetitive sounds around 3 months of age, but that maternal smoking prevents this normal developmental process. What is unclear is whether this altered developmental pathway is due to shared genetic vulnerability (mother and infant have similar genes which predisposes to smoking in adulthood and to altered brain responses in infancy), is a prenatal developmental effect of tobacco exposure (prenatal tobacco alters brain development), or is an acute toxic effect of second-hand smoke. We are conducting experiments to resolve this issue.
The understand the impact of nicotinic mechanisms on early brain development should allow us to develop new treatments, designed to reduce mental illness and the associated high rates of smoking.

Nicotine Addiction

Adams, Catherine
Nicotinic Receptor Role In Hippocampal Development
University of Colorado Health Sciences Center

Smoking during pregnancy causes greater rates of infant death as well as behavioral, learning and memory problems. Animal studies of fetal nicotine exposure have shown similar effects. An area of the brain that influences learning and memory is the hippocampus. The hippocampus is one of the brain regions that is damaged following fetal nicotine exposure. The hippocampal damage may be due to the direct action of nicotine on specific nicotinic targets in the hippocampus known as a7 nicotinic receptors. The first step towards determining whether the changes in hippocampus seen after fetal nicotine exposure are due to the action of nicotine on a7 receptors is to find out whether and how the a7 receptor influences normal hippocampal development. Two different versions of the a7 receptor gene in two different mouse strains have been found to differentially affect the organization of both a7 receptors and interneurons in the hippocampus of the two strains. Specific Aim 1 of this award was to determine whether the different versions of the a7 receptor affected the time course and pattern of development of the a7 receptor in the developing hippocampus of C3H and DBA/2 mice. Data from a completed study show that the a7 receptor appears earlier in hippocampal development in the C3H mouse than in the DBA/2 mouse and that the pattern of development of the a7 receptor in the hippocampus of the two mouse strains is quite different during the period around birth. Congenic mice, mice with the a7 gene of one strain on the other strain's background, are currently being bred to determine whether the differences in a7 receptor development in the two mouse strains is due

to the different a7 receptor gene expressed by the two mice. Studies are currently being conducted on the fetal and postnatal offspring of C3H and DBA/2 mice to determine whether the a7 receptor is expressed on migrating interneurons and/or on interneurons undergoing cell death (Specific Aim 2). Mice without a functional a7 receptor gene (a7 knockout mice) also show differences in the organization of hippocampal interneurons. Therefore, C3H and DBA/2 a7 knockout mouse strains have been developed to determine how the lack of an a7 receptor may influence interneuron migration and death in the developing hippocampus (Specific Aim 3).

Dobelis, Peter

Chronic Nicotine Effects in Mouse Hippocampal CA3 Region

University of Colorado Health Sciences Center

Long term exposure to nicotine, the addictive component of tobacco, results in long term changes in brain function. However, what these changes are and how they are induced at the cellular level is poorly understood. Answering these questions is crucial for understanding and treating nicotine addiction. The studies performed in this proposal focused on identifying which neurons in the hippocampus express nicotinic receptors, and how activation of these receptors affects their function. The hippocampus is one of the brain regions that shows the greatest anatomical changes in response to chronic nicotine exposure in animals models of long term nicotine use, as well as in the brains of human long term smokers. The results of our studies revealed the two major types of nicotinic receptor are expressed in the dentate gyrus region of the hippocampus. The first type has a low affinity for nicotine and is expressed on excitatory and inhibitory neurons. The second type has a high affinity for nicotine and appears to be expressed on some of the inhibitory neurons of this region. Studies examining the effects of these receptors on function in this region suggest that activation of the low affinity nicotinic receptor results in a short term increase in excitability. Stimulation of the high affinity nicotinic receptor results in a relatively long lasting decrease in hippocampal excitability. These results indicate that nicotine has complex opposing effects on hippocampal function, depending on which nicotinic receptor type is being activated. This result raises the possibility for selectively blocking some of the effects of nicotine on brain function. This selective targeting of nicotine effects in the brain may help in the treatment and possible prevention of nicotine addiction. Taken together, these results suggest that nicotine effects in the CA4 region are likely to be complex, affecting both excitatory and inhibitory circuits.

Wehner, Jeanne

Nicotinic Receptor Mediation of Anxiety and Cognition

University of Colorado at Boulder

Recent data indicate that more than 70% of the young people in the United States experiment with tobacco (Kandel et al., 1997) but that less that 30% of adult Americans use tobacco today. These findings indicate that the dramatic decrease in tobacco use seen in the last 30 years is largely due to an increase in the number of people who have stopped smoking rather than to a decrease in the rate of initiation. Therefore, gaining an understanding of those factors that regulate the initiation of tobacco use may be of vital importance for making progress in minimizing tobacco-related health problems. One of the major problems that has kept us from understanding why tobacco is addicting is we do not have a clear understanding of why tobacco (nicotine) is reinforcing although it does not induce euphoria. Smokers frequently claim that tobacco has emotional calming effects, or that it helps them to concentrate. The studies that are funded in this grant have as their major goals establishing whether nicotine does, indeed, have emotional calming effects (reduces anxiety) and whether it enhances concentration (increases attention, learning, memory, cognition). The studies will use several genetic strategies, in part because studies with humans indicate that genetic factors are of importance in regulating the transition from experimentation with tobacco to addiction to tobacco. The studies specifically address which of the many nicotinic receptors mediate the behavioral actions of nicotine.

Data accumulated in the past year indicate that: 1) results from nicotinic receptor mutants indicate that at least two nicotinic cholinergic receptors are expressed in dopaminergic neurons throughout the brain and these regulate nicotinic-stimulated dopamine release; 2.) the mediation of anxiety by the β3 nicotinic receptor is dependent on complex interactions with other genes such that there are marked individual differences dependent on genetic background; 3.) the ability of nicotine to enhance at least one form of learning, contextual learning, is dependent on the expression of the β2 containing nicotinic receptors; 4.) nicotine can enhance appetitive learning and this appears to involve receptors containing α4 subunits. 5.) α7 nicotinic receptors may have a role in regulating

an animal's ability to learn to associate a cue with the appropriate response in situations that require increased attention. 6.) several nicotinic receptor subunits do not appear to be involved in learning or attentional processes including α5, β3, and β4. The cumulative data from both specific aims indicate that there are very specific roles for the different nicotinic receptors in the behavioral actions of nicotine.

Future studies are designed in specific aim 1 to understand the involvement of β3-containing nicotinic receptors in complex gene-gene interactions regulating anxiety and stress responses. Studies will be initiated that examine patterns of gene expression that differ in β3 mutant mice compared to normal mice on differing genetic backgrounds. Studies in specific aim 2 are designed to understand better the roles of α4, β2 and α7 containing receptors in learning and memory and nicotine's enhancement of attention and learning.

By better defining the roles of each nicotinic receptor subtype, it may be possible to target therapies to particular individuals. For example, smokers who use nicotine for its anxiolytic properties might benefit from specific pharmacological directed at the β3 containing receptor while those smokers who use nicotine to enhance attention and cognition might benefit from therapies targeted at the α4β2 type receptors. Additionally, human genetic studies could focus on polymorphisms in particular nicotinic receptor genes and their possible association with anxiety states or attentional deficits.

Prevention & Cessation

Ehringer, Marissa

Candidate Genes for Tobacco and Nicotine Dependence

University of Colorado, Institute for Behavioral Genetics

A number of scientific studies have shown that both environmental and genetic factors play a role in the development of tobacco use. This project involves examining two genes that may contribute to a person's risk for using and becoming addicted to tobacco. These two genes have been studied in mouse models related to nicotine and we are now trying to evaluate their importance in humans. The alpha 4 nicotinic receptor subunit gene (CHRNA4), when it is mutated in mice, is associated with increased signs of anxiety in the animals. Similarly, mice lacking the protein kinase C gamma gene (PRKCG) display more impulsive behaviors than mice that have the gene. In humans, the alpha 4 nicotinic receptor subunit protein is believed to be involved in a person's response to the nicotine found in tobacco products, and different responses in different people may contribute to development of addiction. Similarly, people who are more impulsive may be more likely to try tobacco products than those who are more inhibited, and it is possible this impulsive behavior may be mediated by genes, perhaps the protein kinase C gene. We have been examining variations that occur in the DNA of these genes in a human adolescent sample from Colorado, to see if any of these variations are linked to smoking.

The specific variations we are examining are called single nucleotide polymorphisms, or SNPs, that are differences in one part of a person's DNA. For example, some people might have an "A" form of DNA at the SNP while another person might have a "C" form of DNA. There are many different types of SNPs present in the human population. In the CHRNA4 gene, methods to examine five SNPs have been developed and are being determined in a human adolescent sample. Approximately 150 subjects have been evaluated for each SNP, with approximately 150 more to be examined. For the PRKCG gene, five SNPs have been identified and selected for examination, and the methods for looking at the DNA are being developed. With the current data, there is no evidence for an association between any of the SNPs in the CHRNA4 gene and smoking, but the project is not completed. After the five SNPs in the CHRNA4 gene have been evaluated for each subject's DNA, statistical analyses will be used to determine if specific SNPs are associated with smoking. Similarly, the SNPs in the PRKCG gene will be tested to see if they are associated with the age at which adolescents first tried cigarettes, because this measure may be related to impulsivity.

The aim is to identify specific differences in DNA that are related to the age a person starts smoking or a person's likelihood to become addicted to smoking. Such a finding may help with the identification of kids who are at risk for initiating tobacco use and becoming dependent on nicotine, thereby facilitating direction of early prevention programs. In addition, knowledge about the specific genes may aid in our understanding of the biological mechanisms of addiction in the brain, which could lead to the development of stop smoking treatments.

Helme, Donald W.
Colorado Anti-Tobacco PSA Message Sensation Value Project
The Cooper Institute, Denver

This project examines the premise that the research on televised anti-drug PSA campaigns based on the sensory, affective, and arousal needs of high sensation seekers can be applied to tobacco use to produce media messages that achieve significant changes in tobacco-related attitudes, intentions, and prevention behaviors. The randomized pretest-posttest factorial study will examine this premise among adolescents aged 12 to 14 years. The principle objectives of the study are to test the efficacy of a brief media-based tobacco prevention intervention containing High Sensation Value (HSV) versus Low Sensation Value (LSV) PSAs on producing:

a) attitudes against smoking,
b) intentions not to smoke, and
c) likelihood of acquiring additional advice on how to not smoke (i.e., to prevent uptake or stop smoking) when compared to an intervention containing PSAs lower in message sensation value (LSV).

Currently, the project has completed data collection with approximately 1000 students – 600 in Fall 2002 and 400 in Spring 2003. We plan to continue data collection this fall, gaining an additional 600+ students for the test of the intervention. Preliminary analyses of the data from Wave 1, completed Fall 2002, is presented in this report. Data from Wave 2, completed in Spring of 2003, is not yet ready for analyses.

Jessor, Richard
Tobacco and Alcohol Use in College: A CU Development Study
University of Colorado at Boulder

The key objective of the study is to advance understanding of the role of psychosocial and behavioral risk and protective factors in accounting for degree of involvement in tobacco use and alcohol—including non-use, former use, and current use—among University of Colorado first-year students. The study will also examine the role of psychosocial and behavioral risk and protective factors in shaping the course of development of tobacco and alcohol use over the freshman and sophomore years, including initiation, maintenance/stability, intensification, decline, and discontinuation.

The Year-1 accomplishments of the study include development of the 32-page questionnaire (The Survey of Personal and Social Development at CU), pilot testing of the questionnaire, successful completion of Wave-1 data collection at CU-Boulder and CU-Denver during Fall 2002, processing of the 1328 Wave-1 questionnaires and data file creation, and successful completion of Wave-2 data collection during Spring 2003. Retention rate at CU-Boulder between Waves 1 and 2 was 80%. Retention rate at CU-Denver was 85%.

We now have a firmly established longitudinal study underway, and we are poised to undertake major analyses to address the specific aims of the study. Immediate tasks at the outset of Year 2 include processing of the Wave-2 data and the creation of cross-sectional and longitudinal data files. These data files will then be used in analyses relevant to the specific aims of the study: demonstrating the key role of protective factors in minimizing involvement in tobacco use and moderating the impact of exposure to risk; examining whether the protective and risk factors associated with tobacco involvement are the same as those associated with alcohol involvement; examining whether students who are more involved in tobacco and alcohol use are also less likely to be involved in healthy and more socially positive behaviors, such as regular exercise and volunteer work; assessing the extent to which change in levels of involvement in smoking and drinking is associated with change in risk and protection over time; and assessing whether the pattern of risk and protective factors that accounts for smoking and drinking is similar for men and women, and for older and younger students.

This study constitutes a unique resource for furthering understanding of tobacco involvement among Colorado college students. That understanding can inform the development of intervention programs to prevent or lessen involvement with tobacco and other risk behaviors on Colorado campuses.

Klinnert, Mary D.
ETS Reduction Counseling for Families of Asthmatic Children
University of Colorado Health Sciences Center

Studies of childhood asthma have shown higher percentages and greater severity among low-income, minority children residing in large urban areas. Further investigation has shown that the high rates of asthma were due mainly to low-income status, which in turn is related to social problems and environmental exposures that are

increased in the inner city and are detrimental to asthmatics. Among the detrimental environmental exposures for these children are high levels of cigarette smoke.

There has been clear evidence for some time that passive smoke exposure is associated with increased occurrence of asthma as well as increased severity and health care utilization for those children who have asthma. Based on a comprehensive national survey conducted in 1988-1991, 43% of children in the United States lived in a home with at least one smoker. In comparison, among low-income urban children with asthma, 59% of homes included at least one smoker. Thus, poor urban children with asthma are exposed to high levels of cigarette smoke, which has significant effects on their asthma morbidity.

The goal of the proposed study is to implement an environmental tobacco smoke (ETS) reduction program with the families of these inner-city asthmatic children. To assess whether the program is effective, families who agree to the study are randomly assigned to a group that receives counseling or to a group that receives no counseling. Counselors go to the homes of the families assigned to the counseling group to work with family members on decreasing the amount of tobacco smoke to which their asthmatic child is exposed, but not necessarily on smoking cessation. Counselors work to increase families' knowledge about asthma and impact of cigarette smoke. Subjects will be 132 low- income, predominantly minority children ages two to 13 years with asthma, who are exposed to cigarette smoke in their homes. There are three home-based evaluation sessions: at baseline, post-counseling, and nine months post-counseling. At each evaluation, parents are asked to report the number of cigarettes they have smoked in the child's presence. In addition, the children provide a urine sample, which is tested to see how much nicotine they have in their system. Also, parents are asked to report on their child's asthma symptoms in the past 2 weeks. The children are asked to do a breathing test, which involves blowing into a tube attached to a computer to measure how well they are breathing. Finally, to further examine the effects of counseling, we will compare the number of emergency department visits and hospitalizations in the year before the study to the number of visits post-counseling.

To date 129 families have been recruited for study participation. Baseline assessments have been completed with 96 families. Target children range in age from two to 13 years, with a mean age of 7.3 years. 59% are male and 41% are female. The families are 83% minority. 56% of the families have an income of less than $15,000 per year, 68% of the families receive Medicaid, and 74% of the families are on public assistance. Forty-eight families have been randomly assigned to home-based counseling, and 75% of them have participated fully in the program.

Subject recruitment will continue until the planned number of subjects have been enrolled, counseled, and assessed. If we are able to show that a home-based counseling intervention is effective in reducing the children's smoke exposure and improving their asthma symptoms, such a program may be adopted as the standard of care for smoke-exposed asthmatic children and may be incorporated into public health programs.

Perrine, Nicholas

Motivational Orientations and the Smoking Cessation Process

Colorado State University

There remains much opportunity for the improvement of success rates for formal smoking cessation programs. Even the best formal smoking cessation programs report cessation rates of between 15% and 30%. Following decades of decreases in the smoking rate across the U.S. and Colorado specifically, the smoking rate appears to have reached a plateau in recent years. This research study intends to examine how the environment of an individual who attempts to quit smoking changes overtime. Naturally, people attempting to quit smoking inform their friends and family of their intentions to quit. While friends and family may be encouraging to people attempting to quit, this form of social support will decrease overtime as the struggles of quitting become less obvious. Unfortunately, the smoking cessation process has proved to be a long-term process that requires several trials of success and setbacks. This change in the social support and reward structure is expected to interact with the individual to influence success and failure rates of quitting. Specifically, this study assesses the type of motivational orientations that people adopt in challenging situations and tasks such as quitting. People who are motivated by challenging tasks that require large amounts of effort are considered to have a learning motivational goal orientation. Typically, learning–oriented people are driven to master tasks and find increasing their knowledge about how to better complete a task to be rewarding. People who are motivated by proving to themselves and others that they can complete a task or challenge with very little effort are considered to have a performance motivational goal orientation. Performance-oriented people are motivated by favorable comments from others concerning their ability to perform well at a task without much effort and tend to withdraw from tasks that require large amounts of effort (Button, Mathieu, & Zajac, 1996). These different motivational orientations are expected to interact with the change in social support and reward structure experienced by people attempting to quit. Those individuals with high learning orientations are expected to respond favorable to the change in social support and reward structure. In contrast, those individuals

high in performance orientations are not expected to interact with the change in support and reward structure. Moreover, those individuals who are low on both learning and performance orientations are expected to have the most negative response to the challenge of quitting.

Preliminary results suggest that the social support and reward structure that individuals who attempt to quit smoking must operate within do in fact change over the quitting process. Moreover, results suggest that differences in motivational orientations are responsible for the change in reward structures. People high in the learning orientation tend to report more intrinsic reasons for quitting, which has been linked to favorable success rates in quitting in past research (Curry et al., 1996). People high in performance orientations tend to report both more intrinsic and extrinsic reasons for quitting. In addition, interactions between the motivational orientations and intrinsic and extrinsic reasons for quitting are related to smoking and quit rates three months after receiving smoking cessation services. At the conclusion of the study, it is expected that the motivational orientations will also be useful in predicting those individuals who respond favorably to initial set backs in smoking that are part of the natural course of quitting.

Results from this study are expected to aid health professionals within Colorado to aid smokers in quitting by setting rewards that are consistent with their personal motivational orientation to provide their best chances at quitting. In addition, the results may aid the same health professionals in targeting those quitting smokers who are at risk for negative responses to lapses.

Peters, Annie

Combined Effects of Alcohol and Nicotine

University of Colorado at Boulder

Alcohol and nicotine are two substances that are often used together, even by people do not some cigarettes on a regular basis. Thus, there must be some particularly rewarding aspect to the use of the two substances together. The main objective of this study is to examine the individual and combined effects of alcohol and nicotine on mood and various other subjective variables in order to possibly identify one or more of the reinforcing effects of concurrent use of these two substances.

Although the sample size in this study is currently still small, several interesting effects have emerged. One significant finding is that smoking a cigarette after consuming alcohol is increased subjective feelings of stimulation. Thus, the sedating effect of alcohol may be somewhat reduce by smoking cigarettes. Also, the combination of alcohol and nicotine significantly increased desire to consume more alcohol and to some more cigarettes above and beyond the individual effects of either nicotine or alcohol.

Other variables that are currently being analyzed involve genetic factors, demographic variables, and self-reported history of drinking and smoking behaviors. In addition, cognitive variables relevant to alcohol and nicotine consumption are currently being examined. These analyses may reveal further factors that motivate people to smoke cigarettes while drinking alcohol.

Struhsaker Schatz, Mona C.

Tobacco Use by Foster Care Youth and Professional Responses

Colorado State University

Examining how caseworkers and foster parents view tobacco use among foster care youth and their attention to issues of tobacco use in foster homes was the focus of this exploratory study. Prior to this study, no research existed that examined how smoking behaviors and second hand smoking among foster children (0-18) is responded to by those in professional child welfare practice. Because of the overall well-being of the child is paramount, this research was constructed to examine how this unique risk behavior among some foster children is viewed and responded to by those who have primary responsibility for the child's well-being. Over 500,000 children and youth live in substitute care because of abuse and neglect; roughly 10,000 children are fostered in Colorado each year. Funded by the Colorado Tobacco Research Program, the research used two survey instruments to reach caseworkers and foster parents in both public and private child welfare agencies. The participant population was accessed through both public and private agencies, using both snowball and convenience sampling to achieve the respondent pool. In total, 38 caseworkers and 24 foster parents responded to questions examining a) attitudes about foster care youth who may or may not be smokers, b) practices and responses used with foster care youth around smoking, particularly placement decisions, and c) their won personal smoking behavior and one's personal environment. Findings suggest that much work needs to be done in order to improve how professional caregivers in the foster care

field respond to these youth. Both youth who smoke and foster care children who enter homes where there is smoking in the environment may compromise their overall health and well being. Foster care youth need professionals who will take the time and make reasonable efforts to know what can be done to help the foster child who smokes regularly, as well as the foster child who is at risk due to environmental smoking risks

Swaim, Randall C.
Prediction of Tobacco-Using Groups in Pre-Adolescent Youth
Colorado State University

This project is designed to assess tobacco use, correlates of tobacco use, and friendship patterns over a period of three years among 4th through 6th grade Mexican American and non-Latino white youth. The primary purpose is to identify how social groupings form among youth, and how these groupings, along with other risk and protective factors, serve either to protect youth or place them at greater risk for tobacco use.

During Year 2 we conducted 4 studies to meet the objectives described above:

Study 1: This study examined social predictors of cigarette use, intent to use cigarettes, and confidence in the ability to refuse a cigarette offer. Lifetime use of cigarettes was predicted by number of adults in the home who smoke and cigarette use by peers. Students with two smoking adults in the home were 14 times more likely to have tried cigarettes and nearly 6 times more likely to report intent to use cigarettes compared to students for whom neither parent smoked. Students whose peers smoked were 11.5 times more likely to have tried cigarettes than students who had no friends who smoked. Students who reported that their families had low sanctions against smoking were 44 times more likely to have tried cigarettes and 10 times more likely to report lack of confidence in their ability to refuse a cigarette offer compared to students who reported their families had high sanctions against smoking. Students whose peers who had asked them to smoke were also 10 times more likely to report lack of confidence in their ability to refuse a cigarette offer compared to students who had not been asked to smoke by friends.

Study 2: This study compared two theories, Theory of Reasoned Action and Theory of Planned Behavior in the prediction of cigarette use. Consistent with the Theory of Planned Behavior, perceptions that their peers smoked led to higher intent to smoke and belief in the ability to refuse cigarette offers led to lower intent to smoke. The relationship between intent and actual cigarette use was higher among females compared to males.

Study 3: The third study was not directly related to tobacco use, but was a preparatory study of school characteristics and cross-ethnic friendships among 4th through 6th grad students. Students from two schools completed friendship questionnaires, identifying their five best friends. One school was a neighborhood school with 2/3 White students and 1/3 Mexican-American. The other school was a bilingual immersion school with ½ White and ½ Mexican-Americans. It was hypothesized that Mexican American children in the bilingual school would have more friends who were Mexican American due to the lack of a language barrier. Contrary to our hypothesis, there was a higher degree of cross-ethnic friendships in the neighborhood school compared to the bilingual immersion school. This difference may have been due to differences in acculturation between the two schools, or due to the closer proximity of students in the neighborhood school.

Study 4: The final study examined whether peer influence predicts non-smoking students' image of a typical smoker whether image of a typical smoker predicts their beliefs about the effects of smoking. It was hypothesized that if a student had a positive image of a typical smoker, this image would lead the student to focus on the positive features of smoking and decrease attention to negative consequences of smoking. Peer influences were related to the image of a typical smoker. The more a student perceived that his or her peers smoked and encouraged smoking, the more favorable the individual's image of a typical smoker. Furthermore, the more favorable a students image of the typical smoker, the less likely a student was to report that smoking cigarettes is harmful. These relationships held for both male and female students.

Walkosz, Barbara
Media and Tobacco Education
University of Colorado at Denver

The mass media continue to play a prominent role in the lives of American children and adolescents. A substantive body of research has identified a link between media use and a number of health related behaviors, including smoking. Images of smoking are now well established and prevalent in the narrative structure of popular films and the viewing of these images has been associated with increases in smoking uptake by adolescents. These entertainment narratives are particularly persuasive because of audience identification with characters and the seamless integration of information embedded in the narrative structure. The goals of Project MATE are to develop

a theoretically-based media literacy program to teach students the skills to think critically about, and in the case of smoking, to develop strategies to counter the images presented in the mass media. Media literacy education focuses on the skills of analyzing, evaluating and creating media messages as a means of teaching these crucial critical thinking skills.

Project MATE is in the development/production stages of two interactive web-based media literacy modules that focus on analysis and production skills, respectively, of media messages. Module One examines how smoking imagery is integrated into the narrative structure of films via the role of product placement in entertainment narratives. In this module, students will learn about the film industry and its marketing practices, the marketing of smoking in films, the mediated reality of smoking versus smoking in real life, and how role models, including celebrities who smoke in films, can influence attitudes and behaviors. A key principle in media literacy education is that students not only learn to think critically about film texts but also learn production processes to enhance their analysis skills. In Module Two, using state-of-the-art technology, students will create a short animated film while learning the film production processes of narrative construction, character development and decision-making regarding product placement, particularly smoking, within the film narrative. Further, two databases on smoking imagery in films and a glossary of film industry terms will complement the curriculum.

The next phase of Project MATE will include beta-testing of the web-based modules, development of teacher guides, recruitment of students, and a controlled test of the intervention in the Denver Public school system. The potential impact of this state-of-the-art project for Colorado is such that the project can easily be adapted across the curriculum in all Colorado middle schools in Media Arts, English, Science and Health classes to teach students strategies to counter the persuasive messages about smoking that are embedded in entertainment narratives. The hypothesized of students who receive this curriculum include reduced intention to smoke and smoking uptake for young adolescents.

Yousey, Yvonne K.

Household Factors and Passive Smoke Exposure of Preschool Children

University of Colorado at Denver

Environmental tobacco smoke exposure (ETS) is an important source of illness in preschool children. In spite of the fact that most young children of smokers are exposed at home, little information is available on methods used in families and households to reduce their exposure. Efforts to reduce exposure need to focus on factors, which influence tobacco use of parents and household members. This research identifies smoking policies in households, household characteristics associated with different smoking policies and how they are implemented. It compares self-report of smoking categories of households with cotinine levels of pre-school children living in the home. Understanding factors which contribute to household policies about smoking will assist in developing effective interventions for reducing passive smoke exposure of children.

The specific aims of the research are to:

- Characterize smoking policies in family-controlled spaces.
- Identify factors in households which predict household smoking policies.
- Identify means of implementation of policies in household environments.
- Assess variables associated with ETS exposure (cotinine levels) in children.
- Generate recommendations grounded in the above findings for programs that lead to enhancement of tobacco-free environments for families.

Semi-structured interviews, conducted with 20 parents of pre-school children up to age 4 years, provided preliminary data on smoking rules, policies, and factors in the family, which influenced these policies in household settings. From these data and from review of the literature, a survey instrument was developed to further investigate these factors. The survey is to be piloted, revised, translated into Spanish, and administered to 200 families. Cotinine analysis will be done on one pre-school child in each family. The relationship between household factors, household smoking policies and ETS exposure as reported by family members and cotinine analysis of urine samples of pre-school children will be investigated.

The first three aims of the study are met through completion and analysis of the semi-structured interviews. Variables identified in the literature and confirmed through the interviews include: Health-seeking behaviors in households related to tobacco smoke exposure, health effects of ETS exposure, knowledge, attitudes and beliefs regarding passive smoke exposure, behavioral norms and patterns, and financial investments in health. Demographic data such as socioeconomic status, ethnicity, marital status, household income, size and type of dwelling will be summarized and analyzed as appropriate. These factors are incorporated into a survey

questionnaire, which further investigates household factors impacting smoking policies and methods of implementation of these policies. Data from the survey will be summarized and analyzed to complete the last two aims of the study.

The relationship between household characteristics and smoking categories of households will be investigated with household factors as independent variables and smoking categories in the household as the dependent variable. Translation of the survey into Spanish will expand the number of subjects eligible to participate and increase generalizeability of results. Households who complete the survey and agree to obtain a urine sample for cotinine analysis from a pre-schooler (under age 5) in the home will be reimbursed for their participation.

Data from the semi-structured interviews provide a greater understanding of how families determine and negotiate smoke exposure in the environments in which their children reside. Understanding these data is necessary in the development of effective strategies for dealing with smoke exposure in households. Themes identified in the semi-structured interviews provide the basis for variables to be included in the survey such as knowledge, attitudes, health-protecting behaviors, health effects of passive smoke exposure.

The survey will provide information regarding the importance and significance of factors in the household which impact passive smoke exposure. Measurement of cotinine levels of urine samples of children whose parents complete the survey will allow for further assessment of various factors as they relate to smoking categories in households. The relationship between household factors and smoking categories and smoking categories and cotinine levels will be assessed through multiple regression analysis. Together these will increase our understanding of smoking policies and implementation of policies in households leading to smoke free environments for preschool children.

(f) Recommendations for Future Program Directions

(1) *From the 2002 Annual Report* - ***Partnering with other state tobacco funding agencies***

To better address the public health impact of tobacco and substance abuse, CTRP should evaluate the potential for partnering with state agencies (e.g., State Tobacco Education and Prevention Partnership (STEPP) within the Department of Public Health and Environment) to fund mutually beneficial research projects.

Update for 2003 As detailed in the 2003 CTRP Call for Applications, CTRP offered a new funding mechanism expressly designed for this objective. Jointly funded by the State Tobacco Education and Prevention Partnership (STEPP) and CTRP, CARAs were intended to stimulate and support collaborations between community based organizations (CBOs), or state / local tobacco prevention and control initiatives, with academic investigators to perform scientifically rigorous research into tobacco control issues that: 1) are identified as important to specific communities or subgroups in the state; 2) are likely to produce results that are meaningful to specific communities in the state, STEPP and local community organizations and others involved in implementing similar or related programs and 3) use methods that are relevant, culturally sensitive, and appropriate in terms defined and accepted by the interested communities.

Although we did receive CARA applications, none were sufficiently meritorious for funding this cycle. Should there be funds available for research grants in the future, CTRP would conduct grant writing workshops and other forms of outreach to increase the success rate of applications in this novel area. However, given the absence of future appropriations, no outreach / grant workshops will be conducted.

(2) *From the 2002 Annual Report* - ***Increase the distribution of research dollars geographically across Colorado***

Update for 2003 The CTRP Scientific Advisory Committee considered issuing a Request for Applications centered on providing training grants to Colorado institutions that traditionally focus on undergraduate education. The goal of this RFA would have been to allow undergraduates at institutions lacking extensive research facilities to better prepare for graduate research in areas relevant to CTRP's mission. For example, undergraduate students from Colorado institutions in southern Colorado and the Western Slope could be eligible for summer research internships at Front Range institutions and research centers conducting tobacco- and substance abuse-related research. However, given the termination of appropriations for CTRP, no new initiatives are planned for the future.