Colorado Tobacco Research Program

2002 Annual Report

to the

Colorado Department of Public Health and Environment

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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 Colorado studies and to learn form other state and federal organizations, CTRP also communicates and collaborates with other state tobacco control programs, such as the State Tobacco Education and Prevention Partnership within the Dept. of Public Health and Environment, and is a member of the National Organization of Tobacco Use Research Funders (NOTURF). Several of the emerging trends that influence the setting of CTRP research priorities are:

- Increases in the initiation of smoking in the 18-24 year age group and shifts in adult smoking patterns toward occasional "social" smoking patterns.
- Greater understanding of the health impacts of secondhand smoke in different environmental settings and on different populations, as well as effective approaches for reducing these health risks.
- Smoking prevalence rates in underserved populations and lower socioeconomic classes remain well above the overall state average.
- Common factors underlie individual susceptibility to both tobacco use and substance abuse, underscoring the need for novel approaches to prevention and cessation therapies
- Tobacco-related diseases disproportionately impact the state's health care costs, rendering improved diagnostic and treatment regimens for tobacco-related diseases essential for public health in Colorado.

For both the 2001 and 2002 funding cycles, CTRP adopted the following six research priorities:

- Biobehavioral and Nicotine Addiction Treatment Research
- Biological Research
- Effects of Exposure to Secondhand Smoke
- Epidemiological and Surveillance Research
- Prevention of Tobacco Use
- Policy Research

In 2001, CTRP awarded:

- 14 grants plus the Baseline Evaluation Survey
- for $6.1 million
- at six Colorado institutions

In 2002, CTRP awarded

- 16 grants
- for $6.8 million
- at five Colorado institutions

Introduction

This is the third Annual Report of the Colorado Tobacco Research Program to the Colorado Department of Public Health and Environment, covering the period of July 1, 2001 through June 30, 2002 as mandated in Senate Bill 00-071, section 11, 23-20-208.

By creating the tobacco research fund, the Colorado State Legislature made optimal use of newly available monies to benefit Colorado citizens. Senate Bill 00-071 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 ensures that the research grant program 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 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 two complete funding cycles, CTRP is pleased to report on a total of 28 active research projects as well as one completed project and the conclusion of the Tobacco Attitudinal Baseline Survey (TABS). 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 $12.9 million to fund these new and ongoing projects, CTRP is committed to reducing the physical and mental health impact, and the corresponding economic burden, of tobacco-related diseases within the state.

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 28 Ongoing Grants Made to 6 Institutions

(a) Award Allocation

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

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***
Colorado State University	4 (14)	$927,939 (9)	$678,236	$249,703
Cooper Institute, Denver	1 (4)	$885,740 (8)	$524,107	$361,633
National Jewish Medical & Research Center	4 (14)	$1,901,320 (17)	$1,282,544	$618,776
University of Colorado at Boulder	7 (25)	$3,050,866 (27)	$2,147,823	$903,043
University of Colorado at Denver	2 (7)	$682,480 (6)	$501,647	$180,833
University of Colorado Health Sciences Center	10 (36)	$3,695,970 (33)	$2,552,128	$1,143,842
Totals	**28 (100)**	**$11,144,315 (100)**	**$7,686,485**	**$3,457,830**

(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	12	$4,343,587 (39)
Nicotine Addiction	4	$2,154,698 (19)
Prevention and Cessation	10	$4,039,707 (36)
Mental Health	2	$606,323 (6)
Total	**28**	**$11,144,315 (100)**

The information provided in Table 2 can be restated in the following way: for the first two cycles of CTRP funding, approximately forty percent of the awarded funds are supporting twelve 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. Slightly more than one-third of the awarded funds are

dedicated to ten 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. Approximately one fifth of the award monies support four projects that are investigating the underlying physiological mechanisms that may predispose individual susceptibility to nicotine or play key roles in the progression of addiction. Finally, two 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.

CTRP's Role in Enhancing Research Capacity within Colorado

As detailed in the 2002 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)) and career development awards (i.e., Postdoctoral Fellowships and Dissertation Research Awards). 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 two awards types that are aimed at enhancing the scientific infrastructure for tobacco-related research in Colorado. 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.

Table 3

Award Distribution – by Type of Award

Type of Award	Awards (% of total)	Amount Funded (%)
Independent Investigator Awards		
Research Projects	15 (54)	$10,063,266 (90)
IDEA Projects	6 (21)	$658,165 (6)
Career Development Awards		
Postdoctoral Fellowships	2 (7)	$172,800 (2)
Dissertation Research Awards	5 (18)	$250,084 (2)
Total	**28 (100)**	**$11,144,315 (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, 90% 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, 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.

(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: **$11,073,584**
Other State: **$0**

Though not specified by SB 00-071 reporting requirements, investigators receiving support from CTRP will 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. Since CTRP's funds are derived from the state's share of the national tobacco settlement, the Program seeks to fund research that is particularly significant to tobacco use in Colorado. CTRP aims to be complementary and not duplicative of opportunities available from federal and private funding agencies. The Research Priorities, as developed by the CTRP Scientific Advisory Committee for the 2002 funding cycle as outlined below, reflect this goal.

2002 CTRP Research Priorities

Biobehavioral and Nicotine Addiction Treatment Research

CTRP seeks to fund basic biobehavioral investigations of the biological, psychological, sociocultural, and genetic factors that influence initiation of tobacco use, progression to nicotine addiction, smoking cessation, and relapse; the pharmacological basis of nicotine addiction, including, but not limited to, the role of nicotine receptors in addiction; the appropriate role of nicotine replacement therapies (NRT) in nicotine addiction; research that identifies, tests, and disseminates interventions to treat addicted tobacco users; studies that shed light on how nicotine addiction and disease develop; and explorations of applying the "harm-reduction" paradigm to tobacco use.

Biological Research

CTRP requests studies that strive to reduce the morbidity and mortality from tobacco-related diseases. Appropriate areas include basic disciplines—such as physiology, biochemistry, pathology—as well as translational and clinical investigations that focus on problems associated with tobacco use. CTRP encourages studies that identify and validate biomarkers of tobacco exposure and tobacco-induced cellular events that relate to the different stages of disease progression; define the mechanisms by which tobacco use contributes to disease progression and management; examine the effects of prenatal and postnatal exposure to parental tobacco use; contribute to the understanding of the effects of smoking on our physical and mental health, and discern how these effects may differ by age, ethnicity, race or gender.

Effects of Exposure to Secondhand Smoke

CTRP will fund research that focuses on the biological impact of exposure to secondhand smoke. In addition to research on chronic ailments directly associated with tobacco smoke exposure (e.g., atherosclerosis), studies into the mechanisms, diagnosis or treatment of pulmonary diseases associated with childhood exposure to secondhand smoke (e.g., chronic bronchitis) or exacerbated by secondhand smoke (e.g., asthma) are encouraged. Important in this regard are

quantifying and understanding the chronic effects of exposure to secondhand smoke; and how the impact of exposure to secondhand smoke differs by age and by other demographic factors, emphasizing the need for appropriately designed studies to characterize potentially disproportionate exposures and sensitivities.

Epidemiological and Surveillance Research

CTRP is interested in funding studies that identify differences in host (inherited and acquired), environmental, and behavioral factors that may help elucidate unique contributors to tobacco use and tobacco-related disease. An important and emerging area of research in tobacco use and addiction control is genetic epidemiology. CTRP encourages investigations into the shifting patterns of tobacco use in youth and young adults, smokeless tobacco and cigar use among Colorado teens, and the relationships of illicit drugs to tobacco use. Surveillance and research is needed to monitor and evaluate trends in tobacco use and related disease risk factors, health services, and policy and environmental interventions to determine the influence of these factors on trends in tobacco-related disease incidence, morbidity, mortality, and survival. CTRP also encourages studies that use Colorado's data collections for secondary data analysis.

Prevention of Tobacco Use

CTRP seeks basic and applied social/behavioral research in the prevention of tobacco and substance use. Topics may include, but are not restricted to, tobacco use in schools and communities; experimentation and the casual use of nicotine products; exposure to secondhand smoke; and tobacco usage by mental health populations. Interventions in historically understudied communities or specific racial and ethnic groups to elucidate unique factors and forces shaping their tobacco consumption are invited. CTRP particularly encourages studies that illuminate the resiliency among subpopulations of youth, and that document trends and develop interventions to curb the rise in smoking among young women.

Policy Research

CTRP is interested in funding evaluative research that examines the impact of public policies and program on smoking rates and practices. Included are studies of regulatory policies that limit or discourage access to tobacco products; studies which look at how safety claims for new projects developed by the tobacco industry will be evaluated; research into health care policies and the medical sector's actual and potential role in reducing tobacco in Colorado; and evaluation of efforts to eliminate the tobacco industry's promotions of tobacco products. CTRP also encourages research that documents the role of anti- and pro- tobacco forces in shaping Colorado tobacco policies (e.g. smoke-free bar issues); assessing the impact of the Master Settlement Agreement (MSA) on state and local anti-smoking policies.

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 are provided in Section (e).

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.

2001 Research Projects currently supported by CTRP funding

(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. **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)*** **-** The study uses 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. It is the goal of this study 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.

3. **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 6/30/2003.

4. **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.

5. **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.

Nicotine Addiction

1. **Chronic Nicotine Effects in Mouse Hippocampal CA3 Region, Award #1F-059, *Postdoctoral Fellowship*, $86,400 *(Direct: $80,000; Indirect: $6,400)*** - Investigates 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. **Colorado Anti-Tobacco PSA Message Sensation Value Project, Award #1R-014A, *Research Grant*, $885,740 – *(Direct: $524,107; Indirect: $361,633)*** - 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. **Tobacco Use by Foster Care Youth and Professional Responses, Award #1I-054, *IDEA Grant*, $104,866 *(Direct: $74,958; Indirect: $29,908)* -** This study examines the role of tobacco use among foster children and youth, aged 10-17. Additionally, this study will examine 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 12/31/2002

4. **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.

5. **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 6/30/2003.

Mental Health

1. **Tobacco and Schizophrenia Affect Prenatal Brain Development, Award #1I-051, *IDEA Grant*, $113,250 *(Direct: $75,000; Indirect: 38,250)*** – Focuses 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 12/31/2002.

2001 COMPLETED PROJECTS

1. **Baseline Study Award to provide statistical accuracy of tobacco-related healthcare problems in Colorado, Award #1R-069, $1,499,000 *(Direct: $1,098,168; Indirect: $400,832)*.** The Baseline Study Award was made to Arnold Levinson, Ph.D., from the Center for Research Methodology and Biometry, AMC Cancer Research. The legislatively-mandated study gathered information about tobacco related behavior and attitudes of children/adults in Colorado.

2. **Theory and Research Confounds in Anti-Substance PSA Study, Award #1D-067, *Dissertation Grant*, $20,823 *(Direct: $20,823)*** - Delineated the contemporary history of anti-substance PSA research and conduct empirical studies on their theoretical and methodological weaknesses toward highlighting areas in need of improvement. Principal Investigator - Carson Brandt Wagner, M.A., Doctoral Candidate, University of Colorado at Boulder, School of Journalism and Mass Communication. Mentor - Michael Tracey, Ph.D., Professor, University of Colorado at Boulder, School of Journalism and Mass Communication.

2001 TERMINATED PROJECTS

1. **Nicotinic Signal Transduction in the Central Nervous System, Award #1D-064, *Dissertation Grant*, $46,720 *(Direct: 46,720)*** – Sought to determine a mechanism by which nicotine can result in long-term changes in the brain and provide insights into the origins of nicotine addiction. Principal Investigator - Mr. Liam J. Breeze, Doctoral Candidate, University of Colorado Health Sciences Center, Department of Physiology & Biophysics. Mentor - S. Vijayaraghavan, Ph.D., Assistant Professor, Department of Physiology & Biophysics, University of Colorado Health Sciences Center. Start date 7/1/2001; terminated 12/31/2001 at the request of the Principal Investigator.

2002 Funding Cycle

For 2002, CTRP has 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 last year.

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.

Nicotine Addiction

1. **Alpha-7 Nicotinic Receptor Role in Hippocampal Development, Award #2R-029, *Research Grant,* $524,224 – *(Direct: $399,405; Indirect: $124,819)*** – 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. **Zebrafish: A Model for Nicotine Developmental Toxicity, Award #2R-019, *Research Grant,* $772,324 – (*Direct: $515, 529; Indirect: $256,795)*** – Seeks 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; end date 6/30/2005.
3. **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.

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.

(e) Summary of Research Findings

2001 Tobacco Attitudinal Baseline Survey (TABS)

As stipulated by SB 00-071, the Legislature directed CTRP to "fund evaluative research for the collection of baseline demographic data on tobacco use by persons within the state." [C.R.S. 23-20-206(1)(b)] CTRP awarded the contract for conducting the Tobacco Attitudinal Baseline Study (TABS) to AMC Cancer Research Center (P.I. Arnold Levinson). The TABS survey was the first survey of its kind in Colorado with respect to its extensive sampling and comprehensive inclusion of both youth and adults. Significant findings include the observations that, while the adult prevalence rate is now less than 20% in the state, smoking rates for youth and young adults are increasing.

The data collected from this survey and published in five reports will enable CTRP to develop and refine its research priorities, and assist the State Tobacco Education and Prevention Partnership within the Colorado Department of Public Health plan and evaluate tobacco control programs. These reports are available in PDF format on the CTRP web site at www.cu.edu/ctrp.

TABS reports available in PDF format:

1. Adolescents and smoking: most are trying it, many are hooked
2. Adult smoking: progress and problems
3. Secondhand tobacco smoke: exposures, protections and opinions in Colorado
4. Youth access to cigarettes in Colorado
5. Other tobacco products

Findings of CTRP studies initiated during the inaugural funding cycle

For those projects that just begun on July 1, 2002, 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. 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

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

During the initial ten month funding period of this proposal 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 42 new cases of oral squamous cell carcinoma and 24 cases of oral epithelial dysplasia. We have begun to test 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), and we have evaluated a total of 39 oral cancers, demonstrating telomerase over expression in 31 of them (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.

Huang, Mingxia

Study of the Effect of the Tobacco Carcinogen Benzo(a)pyrene in *Saccharmyces cerevisiae*

University of Colorado Health Sciences Center

This project is 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 are in the process of assessing whether this strain is suitable for the proposed genetic screens.

Panagiotidis, Michail I.

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.

Sievers, Robert E.

CO_2-Assisted Nebulization for Drugs for Lung Ailments

University of Colorado at Boulder

Smoking is the leading cause of both lung cancer and emphysema. Lung cancer is the major cause of cancer mortality. Emphysema is also a serious disease in which the walls of the lung are permanently damaged and weakened, leading to severe breathing problems. In both diseases, the initial site of damage is located in the interior of the lung. Thus, to treat or prevent these diseases, it is necessary for the pharmaceuticals used to reach the lung interior. If these drugs are given systemically in the diet or by injection, relatively high doses are needed to assure that an effective level of the preventive or remedial agents reach the lung's interior. Therefore, there is a great risk of causing side effects in other organs and tissues in trying to deliver enough drugs to have the desired prophylactic or remedial action in the drugs.

Fine dried powders of compounds are ideal vehicles for delivery of therapeutic or preventative agents into the lungs. The University of Colorado has developed and patented a novel method (Carbon Dioxide Assisted Nebulization with a Bubble Dryer®, i.e., CAN-BD process) to make fine dried powders of therapeutic and chemopreventive agents. Our goals in the current research project were to investigate this method for making powders of the protein therapeutic alpha-1-antitrypsin for emphysema and anti-inflammatory chemopreventive compounds to reduce the likelihood of lung cancer.

The goals of this research project are to:

1 Obtain samples of chemopreventive agents (e.g., budesonide, myo-inositol, Celebrex and Vioxx), and proteins such as alpha-1-antitrypsin (AAT) to make inhalable 1 - 3 μm diameter particles for emphysema chemopreventive therapy.
2 Perform parametric studies of fine powder formation.
3 Perform stability and activity studies.

We have accomplished a significant amount of work on Goal 2, using trehalose, sucrose, myo-inositol, NaCl and mannitol as drug models. Respirable micro-particles and nano-particles were synthesized. For Goals 1 and 3, due to the very limited supply of AAT on the open market, we were only able to purchase a small quantity (800 mg) of this protein. Hence, limited AAT experiments were carried out, and the results are reported under Goals 1 and 3. Further progress towards Goal 1 was achieved using two model proteins (trypsinogen and ovalbumin) and two low molecular weight pharmaceuticals (budesonide and myo-inositol, which have been reported to have significant chemopreventive activity). Studies involving budesonide were originally planned for the second year of the project. However, due to the difficulties in obtaining AAT, the budesonide studies were initiated earlier. The AAT studies (fine powder generation, stability and activity) will now become the primary focus during second year efforts, pending the acquisition of adequate amounts of AAT (negotiations continue with two potential suppliers, Arriva and PPL Therapeutics). Parametric studies and budesonide studies will continue in the second year as well.

Silkoff, Philip E.

Inflammation, Oxidative Stress and Dysphasia in COPD

University of Colorado Health Sciences Center

The Colorado Tobacco Research Project at National Jewish looks at the degree of airway inflammation, oxidative stress (chemicals in the airways which cause damage to the lung tissue) and the amount and type of bacteria colonizing the airways (usually there are no bacteria on healthy lungs) in subjects with chronic obstructive pulmonary disease (COPD) due to smoking. Smokers who develop COPD also have a much higher risk of lung cancer compared to smokers without COPD. We are trying to see if the degree of inflammation, oxidative stress and bacterial colonization will be associated with the severity of pre-malignant or malignant changes (dysplasia) in a phlegm sample. Our CTRP project recruits subjects from a new program at National Jewish for the early detection

of lung cancer using a home-collected phlegm sample for pre-malignant or malignant cells and a CAT scan of the chest looking for lung nodules.

IRB approval at National Jewish was obtained for this study on August 28th 2001. The lung cancer detection program started to recruit subjects in October 2001, and recruited 27 subjects, of whom 17 were able to produced good sputum samples. The sputum examinations have shown moderate dysplasia (n=4), mild dysplasia (n= 8), and normal sputum (n=5). The CTRP project has recruited 8 subjects since February 2002. Unfortunately, the lung cancer detection program had to close for lack of public response. After a delay in recruitment in order to obtain National Jewish institutional review board approval on May 29 2002, we are now recruiting subjects for the CTRP study from our patient population at National Jewish and from our clinical research unit. We hope to complete 60 subjects by early 2003.

If airway inflammation, oxidative stress and bacterial colonization are linked to pre-malignant change, then it may be possible to use anti-inflammatory medications or dietary modifications e.g. antioxidants to reduce these factors.

Nicotine Addiction

Dobelis, Peter

Chronic Nicotine Effects in Mouse Hippocampal CA3 Region

University of Colorado Health Sciences Center

Recent reports have suggested that the hippocampal formation plays an important role in drug addiction. The aim of this project is to determine the distribution of nicotinic receptors in the hippocampal formation in order to gain a better understanding as to how acute and chronic exposure to nicotine affects the function of this crucial brain area. The studies described here have been designed to study nicotinic receptor distribution in the CA4 region of the mouse hippocampal formation. The CA4 region contains both excitatory and inhibitory neurons that modulate the activity of the principal neurons of the dentate gyrus and the CA3 region of the hippocampal formation.

Excitatory and inhibitory neurons in the CA4 region are typically identified by their combined anatomical and physiological characteristics. Results of the present study suggest that these two types of hilar neurons that can be distinguished by their intrinsic electrophysiological properties (action potential frequency accommodation) alone. Preliminary data indicate that excitatory mossy cells have a higher instantaneous action potential spike frequency and spike frequency accommodation than interneurons. This represents a novel finding for neurons in the brain region.

Experiments designed to determine nicotinic receptor expression reveal that most hilar neurons express nicotinic receptors with 59/62 neurons responding to nicotinic agonist application. Neurons of both electrophysiological class responded to nicotinic receptor stimulation. This represents a novel finding for neurons in this region of the brain. The pharmacology and kinetics of these responses indicate that they are mediated by nicotinic receptors containing the $\alpha 7$ subunit.

Recently, the compound kynurenic acid (KYNA) has been shown to block $\alpha 7$-mediated responses in rat hippocampal cell cultures. The results presented here indicate that $\alpha 7$ receptor-mediated responses in the mouse CA4 region are insensitive to KYNA. This is a novel finding and suggests that either subtle differences in $\alpha 7$ pharmacology exist between rat and mouse or possibly $\alpha 7$ receptor differences exist between culture and slice preparations.

Taken together, these results suggest that nicotine effects in the CA4 region are likely to be complex, affecting both excitatory and inhibitory circuits. Future studies will examine the effects of both acute and chronic nicotine exposure on neuronal physiology and circuit function in the mouse CA4 region.

Prevention & Cessation

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 work on the first part of designing the intervention materials, that of selecting and coding the anti-tobacco PSAs for levels of Message Sensation Value (MSV). This process was completed in early February of 2002. In May of 2002 the selected anti-tobacco PSAs were utilized in a pretest of the intervention administration protocols and intervention measures with approximately 86 adolescents aged 12-14. Data from the coding process and pretest are being utilized in the development and testing of the computerized intervention materials. Having this form of pretest data provides the project with a strong indicator of intervention material appropriateness and potential message effectiveness with this population. Once the computerized intervention materials have been finalized, they will undergo further pretesting before implementation of the intervention in the cooperating school districts beginning Fall 2002.

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 will be randomly assigned to a group that receives counseling or to a group that receives no counseling. Counselors will 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 will also increase families' knowledge about asthma and impact of cigarette smoke. Subjects will be 132 low income, predominantly minority children ages 2 to 13 with asthma, who are exposed to cigarette smoke in their homes. There will be 3 home-based evaluation sessions: at the beginning, after the counseling, and one year after the counseling has ended. At each evaluation, parents will be asked to report the number of cigarettes they have smoked in the child's presence. In addition, the children will be asked to provide a urine sample, which will be tested to see how much nicotine they have in their system. Also, parents will be asked to report on their child's asthma symptoms in the past 2 weeks. The children will be asked to do a breathing test, which involves blowing into a tube attached to a computer to measure how well they are breathing. As another way to see if the smoke reduction counseling makes a difference, the number of emergency room visits and hospitalizations a child has had for asthma in the year after counseling will be compared with the number from the year before the study.

To date 48 families have been recruited for study participation. Baseline assessments have been completed with 31 families. Target children range in age from 2 to 13, with a mean age of 7.9 years. 31 are male and 17 are female. The families are 85% minority, and 58% have an income of less than $15,000 per year. Of the 31 families who have received the baseline assessments, 15 have been randomly assigned to counseling, and counseling is underway.

The study will be carried out as planned over the next 2 years. 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.

Struhsaker Schatz, Mona C.
Tobacco Use by Foster Care Youth and Professional Responses
Colorado State University

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. Because people's choice to smoke is often related to their feelings of stress and low-self esteem, it was postulated that foster children might smoke at rates above the average youth smoker. Thus, this study sought to learn about smoking issues among foster children and youth, aged 10-17, as well as from two other key sources, namely, the caseworkers who oversee and work for the foster child(ren)'s best interests, and foster parents who provide homes for and nurture these children.

A second question that researchers hope to learn whether professional workers and foster parents help these foster children gain access to smoking cessation and smoking prevention programs. During the first year of this project, staff has distributed two uniquely constructed surveys to a sample group of foster parents and caseworkers. To date responses have been received from both groups. The project staff is waiting until late September to examine the entire data sets in an attempt to work with a larger pool of respondents in these two groups. Access to foster children has become problematic due to limitations on research studies with state wards. At present, a request is in process to Colorado's Attorney General to accomplish this end.

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.

The impact of this project will be to more fully delineate how social groups among pre-adolescents form, and how characteristics of social groups relate to the initiation and use of tobacco. This information will help inform prevention researchers as to how peer influences can be used to prevent tobacco use among youth.

In addition to the grant activities that were described in the first semi-annual report, the primary activity during the remainder of this first project year was completion of initial baseline data collection. A total of 299 4th through 6th grade students from four elementary schools were surveyed. As outlined in the previous report, consent for participation was unacceptably low in two of the schools. For this reason, we have decided to restrict the social network analysis to the two schools for which consent for participation was adequate.

Activities during this period have included:

1. Obtaining a Certificate of Confidentiality
2. Translation of surveys into Spanish
3. Recruitment of schools, parents, and students
4. Finalization of survey instruments, and preparation and programming of reports to be sent to participating schools and data analysis system

We have completed final formatting of survey instruments, purchase of teacher surveys and accompanying software, as well as development of a system for linkage of the four types of surveys that will be administered. Project staff are also completing programming of control files and development of data entry systems for data that will be hand-entered.

The first wave of data is due to be collected between in February, 2002 between the 15th and the 28th. Following collection of the first wave of data, we will begin work on Specific Aims 2 through 7 which relate to analysis of cross-sectional data.

Wagner, Carson B.
Theory and Research Confounds in Anti-Substance PSA Study
University of Colorado at Boulder

Historically, anti-substance public service announcement (PSA) research has investigated the ways in which ads can evoke rational responses, usually among adolescents, that will prevent them from abusing substances such as cigarettes, alcohol, and illicit drugs. A major flaw in this approach is that a good deal of theory and research

suggests unreasoned, "gut feeling" reactions recorded by strength of association (SOA) measures may be more important in predicting behavior. Not only is SOA elicited unobtrusively, but it also conveys the likelihood with which attitudes stored in memory can influence both reasoned and unreasoned choices. This project explored the effects of anti-substance ads on both self-reported attitudes and SOAs through four experimental studies focusing on the peripheral route to persuasion, which is characterized by passive information encoding, and we suggest that this route is most promising for SOA modification due to its associative learning potential.

Results of the first three studies suggest that traditional, self-report change is easier to achieve than SOA alteration and that self-report attitude measures tend to exaggerate PSA effects. More specifically, Studies 1 and 2 examine PSA efficacy in changing self-reported attitudes as opposed to less reasoned responses (as predicted by SOA), and although expressed attitude change was rather easily demonstrated, SOA change could not be similarly detected. (In fact, in Study 2 substance-related SOAs were slightly more pro-substance in the post-ad measure, and this may be due, at least in part, to aroused curiosity.)

Study 3 looks at self-report attitude exaggeration and the impact of an initial response on a secondary one (i.e., testing effects), and results showed that expressed attitude reports tend to exaggerate ad effects and that they are more susceptible to testing effects than are SOA measures.

Study 4 focuses on the effects of persuasion context in SOA change. It looks at the roles of motivation and opportunity to view PSAs on SOAs and self-reported attitude change. In this way, peripheral processing is linked to lower opportunity and/or motivation to view ads, while central processing occurs when adolescents are motivated to watch and have the mental resources and time to pay attention. Mainly, the results of this study show that passive, peripheral message processing leads to more anti-substance SOA as compared to effortful, central processing. Further, the SOA measures better correlated with other, less obtrusive measures responses such as ad celebrity ratings and perceptions of substance-related social norms, and this suggests that they are more veridical, or rather better at measuring truthful attitude responses about substances, which is most likely due to their unobtrusive nature.

In sum, the research highlights theoretical and methodological oversights in prior PSA research toward explaining the gaps that exist between ad intentions and outcomes. Although the processes demonstrated lend promise for using ads to protect youth who face decisions under optimal conditions, the data show that recent PSAs such as the “Truth” and the “terrorism” campaigns might be less useful for adolescents at times when they aren’t rationally making decisions about cigarettes, alcohol, and other illicit substances. Counterintuitively, theory and research suggest that most of the time, rational decision-making is not the default strategy. Based on the results of the four studies, perhaps the best way to use ads to alter unreasoned responses to substances is to simply associate substances with negativity within the ads and to do so in a less dramatic fashion than is currently the norm. Seeking to draw less attention to ads, avoiding elaborate argumentation, and scheduling ads at times when motivation and opportunity to attend to them are low—such as in the late evening hours—would be most effective.

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.

Mental Health

Ross, Randal G.

Tobacco and Schizophrenia Affect Prenatal Brain Development

University of Colorado Health Sciences Center

Prenatal tobacco exposure is associated with long-term impairments in inhibition, whether measured by parental report, formal neuropsychological tests, or physiological response to stimuli. Similar impairments are found in children of parents with severe mental illnesses such as schizophrenia, although it remains unclear whether the impairment in this genetically at-risk group is due to direct genetic factors or is secondary to the genetically-mediated extremely high rates of smoking in parents with schizophrenia. The goals of this IDEA proposal included determining a) when in prenatal development are inhibitory processes first identifiable, b) when in prenatal development is the deleterious effect of tobacco on inhibitory processes first identifiable, and c) are the deleterious effects of tobacco additive to genetic-risk effects or is there an interaction where tobacco effects are even larger in genetically-vulnerable individuals. In the first six months of this project, we have also become aware that the type of stimuli (in our case a pure tone versus "white noise) can effect the physiological response. Thus, we have added an aim to more fully explore this issue, while scaling back on addressing the interaction between genetic vulnerability to mental illness and prenatal tobacco exposure.

One mechanism for assessing prenatal brain inhibitory processes is via prepulse inhibition. When presented with a high intensity stimulus, like a loud sound, there is a characteristic startle response, including arm jerk, eye blink, and elevated heart rate. However, if the intense stimulus is preceded by a threshold level stimulus, e.g. a soft sound, than response to the high intensity stimulus is diminished. Thus, the "prepulse" "inhibits" response to the startle stimulus, and this is known as prepulse inhibition or PPI. PPI is present at birth, but determining the characteristics of the stimulus (e.g. a pure tone versus "white noise") on PPI is not understood (specific aim #1a).

Additionally, it is unclear when, prenatally, PPI develops (aim #2). Although it is known that prenatal tobacco exposure interferes in development of PPI, but not when during development this occurs (aim #2).
In the first year, we have set run several pilot subjects, clarifying what protocol is most effective at this age. For example, we have learned that infants under 4 weeks of age stay in REM sleep during stimulation and are thus optimal for infant studies. We have also learned that when pure tones are used as warning stimuli, responses to startle stimuli are increased, while "white noise" tones appear to be associated with the inhibition we expected. Having clarified the task parameters, we are now working to recruit and run subjects.

The identification of prenatal inhibition, and the factors that impair it, may eventually provide a model for intervention studies aimed at reducing the direct damage of tobacco exposure.

(f) Recommendations for Future Program Directions

(1) *From the 2001 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 2002 As detailed in the 2003 CTRP Call for Applications (*attachment 2*), CTRP is pleased to offer a new funding mechanism expressly designed for this objective. Jointly funded by the State Tobacco Education and Prevention Partnership (STEPP) and CTRP, CARAs are 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.

Future recommendation We will assess the success of this new initiative following the 2003 application review cycle. If needed to increase the success rate of applications in this novel area, CTRP will conduct grant writing workshops and other forms of outreach in time for the 2004 funding cycle.

(2) *From the 2001 Annual Report* - ***Provide information resources on tobacco research issues for both investigators and lay public***

As part of the overall outreach efforts aimed at increasing CTRP's visibility among researchers and tobacco control advocates, CTRP could increase its efforts at information dissemination on both program-specific issues and tobacco-related research on a global scale.

Update for 2002 CTRP now has a user-friendly web address, www.cu.edu/ctrp. Once the new web standards for the CU Office of the President have been established (targeted for Winter 2003), we will incorporate new content on the CTRP web site to address this recommendation.

(3) ***Increase the distribution of research dollars geographically across Colorado***

The CTRP Scientific Advisory Committee is evaluating the potential for 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 be 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. The Committee is also considering other mechanisms as well; e.g., funding research externships for conducting projects in historically underserved areas within the state.

(4) ***Fund research that is complementary to but not duplicative of opportunities from other sources***

Acknowledging that funding from federal sources (e.g., National Institutes of Health) has both enabled some of Colorado's researchers to become internationally competitive and strengthened the state's infrastructure for projects traditionally supported by such opportunities, CTRP seeks to identify and support relevant research that has been underserved by other funding agencies. In particular, CTRP will encourage participatory research that benefits local communities underserved by traditional funding sources, and to increase the Program's emphasis on economic analyses and evaluative research with respect to assessing the effectiveness of Colorado's current tobacco control programs and identifying the fiscal impact of tobacco control policies and tobacco-related disease.

Appendix 1 – 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 2002 annual appropriation: **$6,875,375**

(reflects a reduction of $46,476 as authorized by HB 02-371 which created the Stroke Advisory Board)

(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. As an approximation for 2001-2002, Colorado beneficiaries included the following populations participating in ongoing CTRP research projects:

- 60 pregnant women
- 20 new mothers and their infants
- 48 families with asthmatic children
- 299 primary school students
- 86 adolescents attending middle schools
- 60 adult patients with chronic obstructive pulmonary disease

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 2002, 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 2002 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 is a fiscally prudent alternative to creating an independently designed review process, which would otherwise cost CTRP more money annually than it has in its administrative budget. Outsourcing of the application evaluations also ensures that CTRP will fund 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.

$6,875,375 FY 2002 appropriations to the Colorado Tobacco Research Program

$6,531,606 Expended and/or encumbered for new awards in FY 2002

$ 343,769 Administrative costs incurred for FY 2002

$ 0 Returned to the Tobacco Settlement Trust Fund for FY 2002