Annual Report 2005

Tobacco-Related Disease Research Program

TRDRP

Research for a Healthier Tomorrow

University of California

Annual Report
2005

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from the University of California
to the California State Legislature
on the progress of the
Tobacco-Related Disease Research Program,
established and administered by the University of California
pursuant to Proposition 99,The Tobacco Tax and Health Protection Act of 1988,
Senate Bill 1613 of 1989 and reauthorized pursuant to Assembly Bill 3487 of 1996

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EXECUTIVE SUMMARY

The Tobacco-Related Disease Research Program (TRDRP) is an integral component of California's internationally recognized effort to reduce the severe human and economic toll of tobacco use. TRDRP's mission is to mitigate the impact of tobacco-related illness by funding research on tobacco use and tobacco-related disease. This research has contributed to the success of the state's tobacco control efforts by identifying more effective policies and strategies for tobacco use prevention and cessation, particularly among our state's diverse communities. It has also identified promising new approaches to the treatment of tobacco-related diseases from which Californians suffer. TRDRP identifies the areas in which there is the greatest need for research, funds research that will address these needs, and disseminates the results of the research to the medical, scientific, and tobacco control communities. TRDRP is pleased to be a major contributor to prevention and treatment efforts within the state.

Tobacco consumption in California is at an all-time low due to an effective, comprehensive state tobacco control program and the price of tobacco products, including increases in state excise taxes on tobacco. The Department of Health Services reported that 14.0% of California adults were current smokers in 2005, a 38 percent decline since 1988 when California voters passed Proposition 99, which established the state's comprehensive tobacco research, education, and prevention programs.[1] Despite this decline, research on tobacco-related disease and tobacco use remains important because the state's taxpayers will be paying for decades to come for the treatment of tobacco-related diseases that are now developing in California's current smokers and in adolescents who are starting to smoke. According to a report by the Institute for Health & Aging at the University of California, San Francisco, the cost of smoking in California is nearly $16 billion annually, or $3,331 per smoker every year, an avoidable cost borne by all California taxpayers.[2]

In 2005, 44 research grants were completed, representing cutting-edge science on tobacco-related disease and tobacco control policy and programs, particularly in those groups at highest risk for tobacco use and exposure to secondhand smoke. They included 8 on cancer, 9 on heart and lung disease, 4 on general biomedical and health effects, 7 on nicotine dependence, 5 on secondhand smoke, and 11 on tobacco control, public health and public policy. Brief summaries of the research findings, which appear at the end of this report, include:

- Identified specific molecules in the brain targeted by nicotine; found low rates of tobacco use by Hmong youth and adults;
- Demonstrated the success of an Internet-based smoking cessation program for Spanish speakers;
- Developed a new immunotherapy for the treatment of small cell lung cancer; found that tobacco extract can permanently inhibit the growth of cells from tissue that supports oral tumors;
- Generated antibodies generated that selectively bind to a protein found only in lung tumor blood vessels, which are a potential new means of treating the tumors;

[1] http://www.dhs.ca.gov/tobacco/documents/press/PressRelease04-10-06.pdf
[2] Max, W. et al. The Cost of Smoking in California, December 2002.

- Demonstrated a close association between tobacco smoke exposure and the expression of a gene that leads to the overproduction of mucus in COPD;
- Discovered in internal tobacco industry documents that low levels of sidestream smoke can damage the respiratory epithelium, which contributed to the development of the recent American Society of Heating Refrigerating and Air-conditioning Engineers (ASHRAE) position document which states that the adverse health effects of secondhand smoke cannot be controlled by ventilation;
- Found an increase in smoking cessation that was associated with changes in public policies, particularly physician advice to quit, restrictions on smoking in the workplace and taxation;
- Confirmed that children receive higher doses (amount per pound of body weight) than adults at all levels of activity by modeling the measured particle size distributions of the major carcinogens in sidestream and mainstream tobacco smoke.

In 2005, TRDRP awarded $14.4 million in 55 new grants (3 of which were declined) to scientists at 21 California non-profit research institutions. However, because of insufficient funds, TRDRP was unable to fund 16 research proposals that had been rated "excellent" by expert peer reviewers. The reduced funds for tobacco-related disease research are primarily the result of the decline in revenue from the tobacco excise surtax imposed by Proposition 99.

The largest, multi-year grants addressed the following Primary Research Areas

- Cardiovascular and Cerebrovascular Disease
- Chronic Obstructive Pulmonary Disease
- Development of Nicotine Dependence Treatments
- Lung Cancer
- Prevention and Cessation of Tobacco Use and Tobacco-Related Health Disparities in California's Diverse Populations
- Public Policy and Economics of Tobacco Use
- Secondhand Smoke and Outdoor Tobacco Smoke

INTRODUCTION

The Tobacco-Related Disease Research Program (TRDRP) is an integral component of California's internationally recognized effort to reduce the severe human and economic toll of tobacco use. TRDRP's mission is to mitigate the impact of tobacco-related illness by funding research on tobacco use and tobacco-related disease. This research has contributed to the success of the state's tobacco control efforts by identifying more effective policies and strategies for tobacco use prevention and cessation, particularly among our state's diverse communities. It has also identified promising new approaches to the treatment of tobacco-related diseases from which Californians suffer. TRDRP identifies the areas in which there is the greatest need for research, funds research that will address these needs, and disseminates the results of the research to the medical, scientific, and tobacco control communities. TRDRP is pleased to be a major contributor to prevention and treatment efforts within the state.

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OVERVIEW

Mission

TRDRP's mission is to mitigate the impact of tobacco-related illness by funding research on tobacco use and tobacco-related disease. The program's goals are consistent with the broader mission of Proposition 99, which is to reduce the human and economic costs of tobacco use by reducing the incidence, prevalence, morbidity, and mortality of tobacco-related disease in California.

Goals

TRDRP strives to meet the needs of the research community, the tobacco control community, the health care community, policy makers, and the public by:

- Funding high-quality and innovative research that contributes to the understanding of tobacco use and tobacco-related illnesses and serves California's diverse populations.

[1] http://www.dhs.ca.gov/tobacco/documents/press/PressRelease04-10-06.pdf
[2] Max, W. et al. The Cost of Smoking in California, December 2002.

- Serving as an information resource for tobacco issues through dissemination of research findings and sponsorship of conferences and symposia.
- Funding research that will lead to more effective disease treatments for California's smokers and former smokers.
- Funding research that will lead to more effective strategies for tobacco use prevention and cessation.

TRDRP strives to meet additional needs of the research community by:

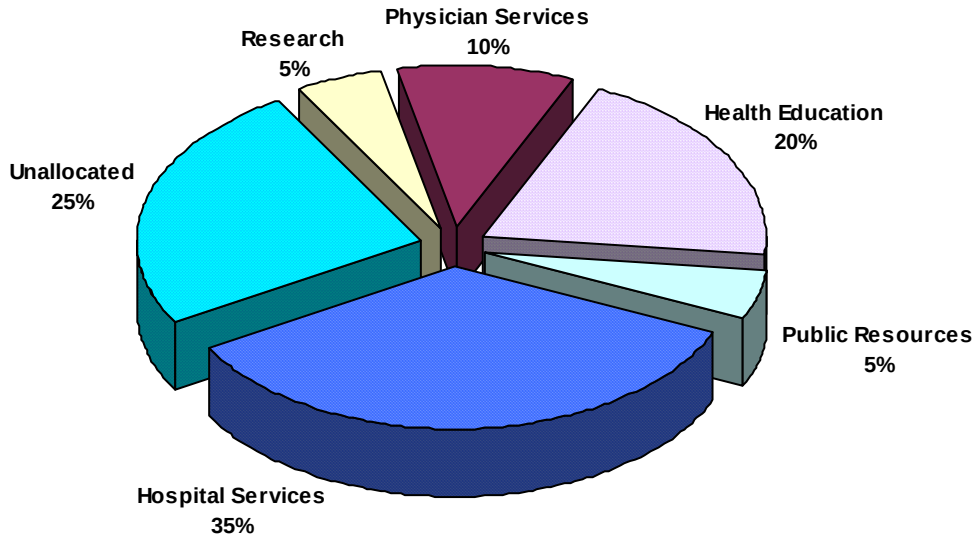
- Providing opportunities to researchers to conduct high quality and innovative research that advances tobacco-related science.
- Helping to build the research infrastructure in California that is critical for comprehensive tobacco-related disease research, in part by encouraging investigators to pursue careers in tobacco research through career development grant awards.

Program Administration

TRDRP was established as a result of the passage of Proposition 99 ("The Tobacco Tax and Health Protection Act of 1988") in November 1988. The proposition increased the tax on cigarettes by 25 cents per pack and raised the tax on other tobacco products an equivalent amount. The initiative created the Cigarette and Tobacco Products Surtax Fund, consisting of six accounts in which specific percentages of the revenue are deposited annually (see Figure 1): the Research Account (5 percent), the Health Education Account (20 percent), the Hospital Services Account (35 percent), the Physician Services Account (10 percent), the Public Resources Account (5 percent), and the Unallocated (or General Purposes) Account (25 percent). Collection of the tax began on January 1, 1989.

Proposition 99 specified that the revenues from the Research Account be used to fund research on tobacco-related disease in California. The California Legislature subsequently asked the University of California to establish and administer a research program to facilitate the elimination of smoking in California, and to report annually to the Legislature about the activities of the Program. TRDRP manages all fiscal and programmatic aspects of the tobacco research funding from the Cigarette and Tobacco Products Surtax Fund. As stipulated by the legislation, funding for administrative expenses is limited to five percent of the Research Account. Within the Office of the President at the University of California, TRDRP is one of the Special Research Programs in the Office of the Provost and Senior Vice President for Academic Affairs.

Figure 1. Distribution of Tobacco Tax Revenue Specified by Proposition 99



REPORT ON 2005 ACTIVITIES

Completed Grants

In 2005, 44 research grants were completed, representing cutting-edge science on tobacco-related disease and tobacco control policy and programs, particularly in those groups at highest risk for tobacco use and exposure to secondhand smoke. They included 8 on cancer, 9 on heart and lung disease, 4 on general biomedical and health effects, 7 on nicotine dependence, 5 on secondhand smoke, and 11 on tobacco control, public health and public policy. Brief summaries of the research findings, which appear at the end of this report, include:

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- Confirmed that children receive higher doses (amount per pound of body weight) than adults at all levels of activity by modeling the measured particle size distributions of the major carcinogens in sidestream and mainstream tobacco smoke.

Research Involving Women and Communities of Color

Of TRDRP's 202 active grants, 66 (33 percent) involve human subjects. Of these, 62 (31 percent) involve women subjects and 62 (31 percent) involve subjects from communities of color. An additional 14 grants are conducting secondary analyses of data originally collected from human subjects. All six of these involve both women subjects and subjects from communities of color.

TRDRP Coordination with Tobacco Control and Education Programs Funded by the Proposition 99 Health Education Account

TRDRP coordinates its activites with the California Department of Health Services (DHS) and the California Department of Education (CDE) because the three agencies share the mission of reducing the harm and costs of tobacco use in the state. They receive funding from a common source, the Cigarette and Tobacco Products Surtax Fund created by Proposition 99. During 2005, TRDRP staff continued to work with their counterparts from the DHS Tobacco Control Program and the CDE Safe and Healthy Kids Program Office to keep abreast of developments in their respective programs, avoid duplication of effort, share expertise, and provide input into the development of each program's goals. CDE and TRDRP jointly re-issued a revised Request for Applications to fund an evaluation of the "*I Decide* Teen Tobacco Cessation Program" which is being used in a number of California school districts.

Dissemination of Research Findings

In accordance with state statutes, TRDRP regularly disseminates the findings of funded research in a number of ways. The knowledge gained from TRDRP-funded studies is helping to improve the effectiveness of the tobacco control programs supported by the Proposition 99 Health Education Account that are administered by the California Department of Health Services and the California Department of Education. Results of research on tobacco-related disease are also enhancing scientists' understanding of biological mechanisms underlying the cause of tobacco-related disease and pointing the direction to technologies for the earlier detection and more effective treatment of lung disease, heart disease, and cancer.

- **Scientific Publications**

TRDRP-funded investigators have continued to actively disseminate findings from their research in scholarly publications and at scientific conferences. In 2005, funded investigators reported publishing 206 articles in refereed scientific journals, including 146 that had appeared in print and 60 that were accepted for publication and were awaiting appearance in print. Some of the peer-reviewed scientific journals in which the papers appeared include: *Addictive Behaviors; American Journal of Epidemiology; American Journal of Physiology; American Journal of Public Health; American Journal of Respiratory & Critical Care Medicine; Angiogenesis; Biophysical Journal; Birth Defects Research; Brain Research; Cancer Epidemiology,*

Biomarkers, and Prevention; Cancer Research; Clinical Cancer Research; Cardiovascular Research; Cell; Chest; Circulation; Environmental Science and Technology; FASEB Journal; FEBS Journal; Health Economics; Heart Rhythm; Journal of American College of Cardiology; Journal of Biological Chemistry; Journal of Consulting and Clinical Psychology; Journal of Immunology; Journal of Neuroscience; Journal of Neuroscience Research; Molecular Biology of the Cell; Nature Structural & Molecular Biology; Nicotine and Tobacco Research; Oncogene; Placenta; Preventive Medicine; Proceedings of the National Academy of Sciences USA; Science; Tobacco Control and *Toxicological Sciences.*

- **Biennial Scientific Conference 2005**

Scientific conferences are one of the most effective ways to disseminate recent research findings in a timely manner. TRDRP has hosted conferences at which its funded investigators report their latest findings. The program has expanded the traditional scientific conference model by including tobacco control professionals to give them the opportunity to learn about the latest findings directly from the scientists who are conducting the research.

More than 400 researchers and tobacco control practitioners attended TRDRP's Biennial Conference in Los Angeles on October 10-11, 2005. The conference theme was "15 Years of Progress in the Fight Against Tobacco." The Opening Session was highlighted by a talk on the legislative perspective on tobacco control in California by the Honorable Wilma Chan, California State Assemblywoman, and a keynote address, "Tobacco Industry Research: The Good, The Bad, and the Bias," by Professor Lisa Bero of the University of California, San Francisco. The Plenary Session included talks by four of the nation's leading scientist/clinicians on heart and lung disease, smoking cessation treatment advances, and the latest technology for imaging the effects of nicotine on the brain. Former UC Vice President for Health Affairs Cornelius L. Hopper, M.D. gave an inspiring speech on challenges facing prospective tobacco-related disease researchers from diverse communities.

A new conference feature was the Tobacco Research Translation Institute (TRTI), which was designed to facilitate the dissemination of research findings to tobacco control professionals and the larger public health community. The TRTI sessions presented the latest scientific findings on the reproductive health effects of secondhand smoke exposure and provided a forum for a dialogue between leading scientists in this research area and tobacco control professionals. In addition, each TRTI participant was provided with a tool kit designed to aid them in using the scientific content in their public health practice. Approximately 70 took advantage of this unique opportunity.

Scientists presented the latest findings of their TRDRP-funded projects at twelve scientific sessions, including research using tobacco industry documents, public policy for tobacco control, secondhand smoke, nicotine dependence, smoking cessation, menthol cigarettes, adverse reproductive health effects, heart disease, lung disease, and cancer.

- **Newsletter**

In 2005, TRDRP published three issues of its newsletter, *Burning Issues*, which contained articles on critical research topics in tobacco-related disease and tobacco use, and information about the program and notices of upcoming events. They included articles on the Cal EPA's

designation of secondhand tobacco smoke as an air pollutant, growing hookah use in the State and nationwide, and the development of nicotine vaccines. The newsletters are posted on TRDRP's website (http://www.trdrp.org/Newsletters.asp).

- **Website**

Visitors to TRDRP's website (www.trdrp.org) can search research grants, as well as view all program publications and announcements.

- **Collaborations**
  - TRDRP co-sponsored the *2nd East-West Conference on Tobacco & Alcohol: Culture, Environment, and Genes* on April 5-6 in Pasadena. The conference was organized by the University of Southern California's Institute for Health Promotion & Disease Prevention Research. Approximately 150 scientists from 9 countries participated.
  - TRDRP organized and sponsored a research session, "The Science behind Secondhand Smoke," on September 17 at the *American Lung Association of California's Annual Conference* in San Francisco. Two TRDRP-funded investigators, Brett C. Singer, Ph.D. of Lawrence Berkeley National Laboratory and Wayne Ott, Ph.D. of Stanford University, provided a scientific perspective on smoke free housing issues.
  - TRDRP was a primary sponsor of the conference, *Frontiers in Aerosol Dosimetry Research* on October 24-25 at the Beckman Center of the National Academies of Science and Engineering in Irvine. Approximately 90 scientists from 12 countries participated.

- **Staff Extramural Activities**

During 2005, TRDRP staff participated in a number of national, state, and local conferences to report on program activities, learn the latest scientific developments, and network with scientists who are potential applicants or peer reviewers.

Dr. Kamlesh Asotra

- Gave a plenary lecture, "Tobacco Smoking-Induced Cardiovascular & Cerebrovascular Diseases" at *ISARCOM 2005, International Conference/CME, 18th Annual Meeting of the Indian Society of Atherosclerosis*, Lady Hardinge Medical College in New Delhi, India, in November.
- Organized and chaired the "Californian Symposium" at the *World Assembly on Tobacco Counters Health (WATCH) International Conference* in New Delhi, India in December.
- Organized an international conference on *Tobacco-Related Diseases: Global Public Health Challenges in the 21st Century* and gave the Professor Surender S. Katoch Memorial Lecture, "University of California Tobacco-Related Disease Research Program: 15-Year Experience and Achievements in the Fight Against Tobacco in California and Global Implications" at the School of Life Sciences, Jawaharlal Nehru University in New Delhi, India in December.

Dr. Francisco Buchting

- Gave an invited address, "The Disparate Burden of Tobacco in LGBT Communities" at the National Cancer Institute's meeting of the Tobacco Research Network on Disparities (TReND) in February in Pasadena.

- Organized a 90-minute session on research highlights featuring four TRDRP-funded projects at the *2005 Project Directors' Meeting* sponsored by the California Department of Health Services' Tobacco Control Section on April 20-21 in Sacramento. Then-TRDRP Director, Dr. Charles DiSogra, was the moderator and discussant.
- Participated in the National Cancer Institute's meeting, *Challenges in Tobacco Industry Documents Research* on May 1 in Chicago.

- Gave a presentation on "Implementing the National LGBT Communities Action Plan and the Disparate Burden of Tobacco in LGBT Communities" at the *National Conference on Tobacco or Health* held the week of May 2 in Chicago.

- Gave an invited talk, "Understanding the Impact of Tobacco and Cancer in Latino Communities in California" at an American Cancer Society *Doctor's Talk* in December in Oakland.

- Spoke on "From Research to Action: Advancing Research Translation in Tobacco Control" at *133rd Annual Meeting of the American Public Health Association* in December in Philadelphia.

Dr. Phillip Gardiner

- Co-presenter on "African American Utilization of the California Quit Line" at the *Southern California Cessation Consortium* in February in Los Angeles.

- Chaired the Participatory Research Study Section of the Minnesota Partnership for Action Against Tobacco (MPAAT) in March in Minneapolis.

- Co-chaired a synthesis and discussion panel at the *2nd East-West Conference on Tobacco & Alcohol: Culture, Environment, and Genes* in April in Los Angeles.

- Facilitated a scientific session reviewing the use of telephone quit lines as a tool in tobacco cessation among distinct racial and ethnic populations at the *National Conference on Smoking OR Health* in May in Chicago.

- Gave a guest lecture on "Tobacco Use in the African American Community and Among Women" at the University of Washington's Center for Health Education and Research, Tobacco Studies in Public Health and Tobacco Scholars Program in May in Seattle.

- Gave an invited talk to the Tobacco Cessation Task Force at the Watts Health Center in June in Los Angeles.

- Gave a luncheon speech on "African Americans, Health Disparities and Tobacco Use" at the *Mayo Clinic Nicotine Dependence Conference* in October in Rochester, Minnesota.

- Gave an invited address on "African Americans and Mentholated Cigarettes" at the *Ohio State-wide Conference on Tobacco Control* November in Columbus, Ohio.

Dr. Charles L. Gruder

- Served on the Research Funding Advisory Panel of the Minnesota Partnership for Action Against Tobacco (MPAAT) in April in Minneapolis.

2005 FUNDING CYCLE

- **Research Grants Awarded**

In 2005, TRDRP awarded $14.4 million in 55 new grants (3 of which were declined) to scientists at 21 California non-profit research institutions. However, TRDRP was unable, because of insufficient funds, to fund 16 research proposals that had been rated "excellent" by expert peer reviewers. The reduced funds for tobacco-related disease research are primarily the result of the decline in revenue from the tobacco excise surtax imposed by Proposition 99. Details of 2005 awards, including abstracts, can be found in TRDRP's Compendium of Awards, which can be accessed at http://www.trdrp.org/Docs/Compendiums/Compendium2005.pdf or obtained from the program office (trdrp@ucop.edu or 510-987-9870).

The largest, multi-year grants addressed the following Primary Research Areas

- Cardiovascular and Cerebrovascular Disease
- Chronic Obstructive Pulmonary Disease
- Development of Nicotine Dependence Treatments
- Lung Cancer
- Prevention and Cessation of Tobacco Use and Tobacco-Related Health Disparities in California's Diverse Populations
- Public Policy and Economics of Tobacco Use
- Secondhand Smoke and Outdoor Tobacco Smoke

- **Award Types**
  - **Research Project Awards** fund investigator-initiated research projects on all aspects of tobacco-related disease and tobacco use. These awards support research that is judged likely to yield valuable outcomes. The projects are judged to be feasible and likely to succeed because they employ sound scientific approaches and offer promising supporting data from preliminary studies.
  - **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 career development awards.** TRDRP offers three award types that are aimed at enhancing the scientific infrastructure for tobacco-related research in California by supporting the development of careers in research. **New Investigator Awards** are aimed at encouraging newly independent investigators to conduct research on tobacco-related issues**. Postdoctoral Fellowship Awards** allow researchers early in their careers to receive training in tobacco-relevant disciplines. **Dissertation Research Awards** provide support for the dissertation research of doctoral candidates who wish to pursue tobacco-related research.

- **Collaborative research awards. Community-Academic Research Awards (CARA)** are intended to stimulate and support collaborations between community-based organizations and university-based investigators to perform scientifically rigorous research into tobacco control issues important to California's diverse communities. **School-Academic Research Awards (SARA)** are intended to stimulate and support collaborations between schools and university-based investigators to perform scientifically rigorous research into tobacco control issues that: 1) are identified as important to schools in the state; 2) are likely to produce results that are meaningful to school-based prevention and intervention efforts; and 3) use methods that are relevant, culturally appropriate, and appropriate in terms defined and accepted by the schools. SARAs are jointly funded by the California Department of Education (CDE) and TRDRP.

- **Cornelius Hopper Diversity Award Supplements**

The Cornelius Hopper Diversity Award Supplements (CHDAS) are designed to encourage TRDRP-funded principal investigators to mentor individuals who want to pursue careers in research on tobacco use and tobacco-related disease. Qualified applicants for the CHDAS are from groups that are underrepresented among researchers who investigate tobacco use or tobacco-related disease, and/or individuals who will work directly with underrepresented groups that are disproportionately impacted by tobacco use. Three funded investigators received supplements to their TRDRP grants for support of new project personnel (see Table 2).

Table 2. CHDAS awarded in 2005

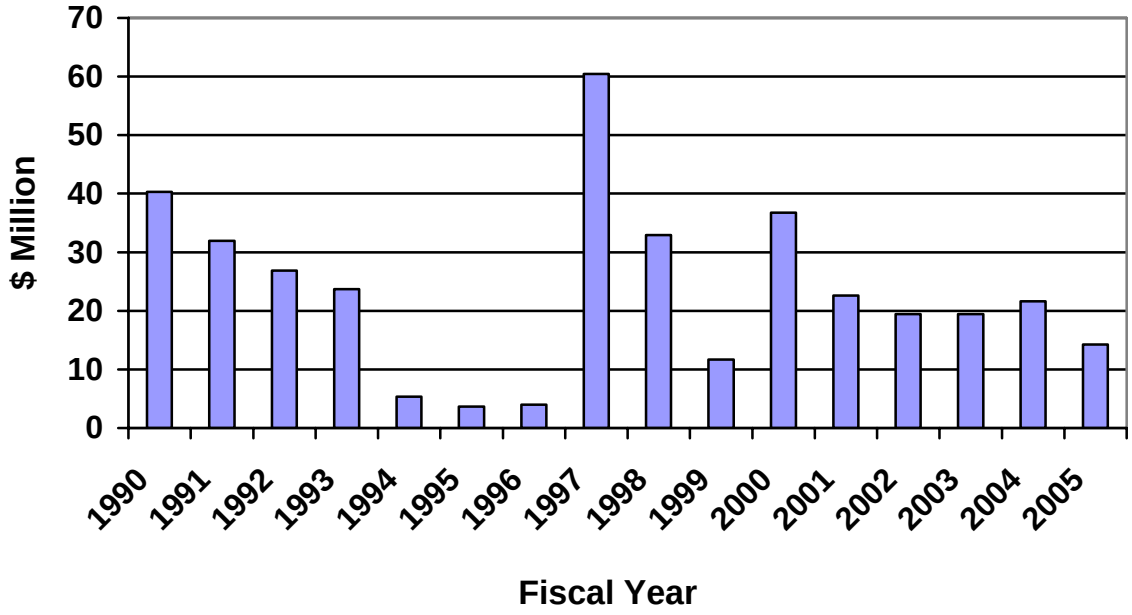
Trainee	*Mentor*	*Institution*	*Grant title*
Maria Herrera	Dr. Ricardo Munoz	University of California, San Francisco	Internet health research center: smoking, Latinos, and the web
Minal Patel	Dr. William McCarthy	University of California, Los Angeles	Ethnicity and school-level effect on California student tobacco use
Jessica Wong	Dr. Jacquelyn Gervey-Hague	University of California, Davis	Chemotherapeutic inhibition of polysialic acid biosynthesis

HISTORY

Appropriations

The sole source of TRDRP funds is the revenue from the tobacco surtax that was established when California voters passed Proposition 99 in 1988. Proposition 99 specified that five percent of this tax revenue be deposited in the Research Account and that it be used exclusively for research on tobacco-related disease. Tobacco sales in California have steadily declined since the Proposition 99 tobacco excise surtax went into effect in 1989. Between 1990-91 and 2004-05, TRDRP resources declined from $26.9 million to $14.3 million annually. Appropriations from the Research Account to the University of California have shown large fluctuations – from $40.3 million in 1990 to $3.65 million in 1995 to $60.4 million in 1997 (see Figure 2).

Figure 2: Appropriations to TRDRP from Proposition 99 Research Account, 1990-2005



Starting in 2000-2001, the amount appropriated from the Research Account to the California Department of Health Services was increased from approximately $1.7 million to approximately $5 million annually. During the first ten years of Prop. 99-funded programs, the annual appropriation to DHS remained at approximately 6 percent of available funds (i.e., revenue, interest, and Proposition 10 backfill), regardless of the amount appropriated to UC. For example, in 1999-2000 it was 7.5 percent. Starting in 2000-2001, however, the DHS appropriation was increased to approximately $5 million which is now 24 percent of the total available.

Grants Awarded

Since its inception in 1989 through 2005, TRDRP awarded $360 million in 1,120 grants to approximately 800 scientists at 80 California institutions. The grants awarded constituted 24 percent of the applications received. The dollar amounts and number of grants awarded by subject area are displayed in Table 1.

Table 1. Award Totals by Subject Area, 1989-2005

Subject Area	*Number of Awards*	*Amount ($)*
Cancer	217	58,394,922
Cardiovascular Disease	137	42,761,076
Epidemiology	145	56,367,753
General Biomedical Science	121	30,640,290
Nicotine Dependence	123	34,351,712
Public Health/Policy	115	31,039,120
Pulmonary Disease	138	38,716,964
Tobacco Control	124	52,450,430
Total	**1,120**	**359,158,548**

Evaluation of Research Grant Applications

Research grant proposals submitted in response to TRDRP's Call for Applications are first screened for relevance to the program's mission. Relevant proposals are assigned to a committee of peer reviewers who are experts in the scientific discipline and subject matter of the proposed research (these committees are known as "study sections"). Peer reviewers are drawn from outside California to minimize actual and apparent conflicts of interest with the applicants. Each study section evaluates applications for their scientific merit. Following state statutes, the evaluation procedure is modeled on the one used by the National Institutes of Health. The study sections' merit ratings are transmitted to TRDRP's Scientific Advisory Committee (see below). The committee uses the scientific merit ratings together with the degree to which a proposal is responsive to funding priorities to make funding recommendations. The awards recommended for funding by the Scientific Advisory Committee represent important and innovative research that promises to advance knowledge needed to improve tobacco control; tobacco use prevention and cessation; protection from secondhand smoke; and prevention, treatment, and diagnosis of tobacco-related disease.

SCIENTIFIC ADVISORY COMMITTEE

In accordance with enabling legislation, a Scientific Advisory Committee advises the University on the administration of TRDRP. Members, who represent major California organizations involved in health research, are appointed to three-year terms, are not compensated, and may not receive TRDRP funding while serving on the committee (see Table 3). The committee is charged with recommending the strategic objectives and priorities of TRDRP and with making final recommendations on grants to be funded based on the established priorities and the scientific merit of the proposals as determined by peer review.

Table 3. Scientific Advisory Committee Roster, 2005

CHAIR	*REPRESENTING*	*TERM*
Thomas Scott, Ph.D. Vice President for Research San Diego State University 5500 Campanile Drive San Diego, CA 92182	Tobacco-related disease research institution	2004-2007
MEMBERS		
Roshan Bastani, Ph.D. Professor & Associate Dean for Research School of Public Health and Jonsson Comprehensive Cancer Center University of California, Los Angeles Room A2-125 CHS, Box 956900 Los Angeles, CA 90095-6900	Behavioral and social research	2003-2006
Carlene E. Henriques, CHES Program Coordinator Sacramento County DHHS Tobacco Education Project 9719 Lincoln Village Drive, Suite 300A Sacramento, CA 95827	Community-based provider of health education and prevention services	2005-2008
Fredric B. Kraemer, M.D. Professor of Medicine Division of Endocrinology Stanford University Medical Center Stanford, CA 94305-5103	American Heart Association, Western States Affiliate	2005-2008
Paul Murata, MD, MSPH Medical Institute of Little Company of Mary 20911 Earl Street, Suite 400 Torrance, CA 90503	American Cancer Society, California Division	2005-2008
Geraldine V. Padilla, Ph.D. Professor & Associate Dean for Research UCSF School of Nursing 2 Koret Way, Room N339 San Francisco, CA 94143-0604	Professional medical or health organization	2005-2008
Gerd P. Pfeifer, Ph.D. Professor of Biology Beckman Research Institute, City of Hope 1500 E. Duarte Road Duarte, CA 91010	Biomedical research	2004-2007

Kim D. Reynolds, Ph.D. Associate Professor Institute for Health Promotion & Disease Prevention Research Keck School of Medicine University of Southern California 1000 South Fremont Avenue, Unit 8 Alhambra, CA 91803	Independent research university	2005-2008
Randall S. Stafford, M.D., Ph.D. Associate Professor of Medicine Stanford Prevention Research Center Stanford University Medical School Hoover pavilion, Room N229 211 Quarry Road Stanford California 94305-5705	Independent research university	2005-2008
Ken Yoneda, M.D. Associate Professor Division of Pulmonary and Critical Care Medicine University of California, Davis 4150 V Street, Suite 3400 Sacramento, CA 95817	American Lung Association of California	2003-2006

RESULTS OF FUNDED RESEARCH

This section highlights the research findings from grants that ended in 2005.

Nicotine Dependence

Nicotine withdrawal, smoking & cognition: An fMRI study (10RT-0091)
Edythe D. London, Ph.D.
University of California Los Angeles
This project advanced our understanding of nicotine dependence and efforts to develop smoking cessation treatments. It used behavioral tests and functional magnetic resonance imaging (fMRI) to investigate the extent to which smokers' ability to focus attention is impaired and affected by withdrawal and acute smoking. Both smokers and nonsmokers made more errors on a task which required greater attention than one that required less focus, and abstinent smokers responded more slowly than nonsmokers on both types of task. Smokers, but not nonsmokers, showed distracting effects by responding more slowly to smoking-related words than to neutral ones. Smokers also responded more slowly overall when abstinent than when sated, but faster after smoking a cigarette during a break. Nonsmokers performed more slowly after the break. These findings suggested that perceived inability to concentrate during withdrawal is not specifically related to focusing attention and that improvement in performance after acute smoking is not related specifically to focusing attention.

The fMRI scans were used to identify brain areas that may mediate effects of smoking and withdrawal on attention. Nonsmokers showed similar patterns of brain activation on a task which required greater attention than one that required less focus, with activation in prefrontal and parietal cortices, and the striatum. However, they showed more activation of the left inferior frontal cortex while performing the task that required greater attention. Prior findings have indicated that this brain region contributes to suppression of word-related distracters. Smokers showed reduced activity in the right superior frontal cortex related to selective attention after a smoking break, but nonsmokers showed no change after a break. As the right superior frontal cortex has been implicated in shifting of attention, this finding suggested that smoking enhanced the efficiency of brain function, requiring less activity associated with suppressing distracters and focusing of attention. While smoking a cigarette did not improve performance significantly, fMRI was a more sensitive measure, providing evidence that smoking affected the efficiency of brain activation related to attention focusing in smokers.

Neurobehavioral consequences of adolescent nicotine exposure (10RT-0334)
Cindy L. Ehlers, Ph.D.
The Scripps Research Institute
The initiation of smoking during adolescence may have dramatic long-term consequences on health care costs. It has been suggested that the findings of poorer outcome associated with the early onset of tobacco use may be related to the fact that smoking is "more addictive" when a person begins smoking during adolescence. Although the reasons for this higher risk for addiction to smoking during adolescence are not entirely understood, it is likely due to the fact that the brain goes through rapid and dramatic physical and physiological changes during that time. These developmental brain processes, although critical for adult development, may put the adolescent brain "at risk" for drug abuse and/or the toxic effects of nicotine and other drugs. It seems that changes that occur in the adolescent brain may resemble in some ways another critical time in development that occurs during late fetal development. This study found in an animal model that adolescent exposure to nicotine increases anxiety-like behavior and produces hypoactivity during adulthood. It is speculated that stress and anxiety play important roles in the maintenance of smoking, since abstinence increases these factors, thus laying a basis for continued or chronic adolescent nicotine use to alleviate the negative symptomatology.

Brain gene expression imaging in nicotine addiction (11RT-0172)
Desmond J. Smith, Ph.D.
University of California at Los Angeles
To better understand the genetic changes that occur in the brain as a result of addiction to nicotine, this study devised a new method called "voxelation." This technology combines rapid gene expression techniques with the mathematical foundations of CT (computed tomography) and PET (positron emission tomography) scanning. It is as if, instead of just one type of X-ray, there were thousands of different "types" of X-ray beam, each beam capable of tracking a different gene and providing a vivid 3-D image of its expression pattern. Experiments were conducted using the voxelation technology to identify the genetic changes that occur in the brain of an animal model as a result of chronic exposure to nicotine. This study demonstrated that the voxelation method could detect specific genes that are involved in nicotine addiction. As voxelation is improved, registration between the underlying neuroanatomy and the harvested

voxels becomes increasingly important. Genes identified as being involved in nicotine addiction can be used by scientists to develop drugs that can break the addiction cycle.

Nicotinic receptors and Parkinson's disease (11RT-0216)
Maryka Quik,, Ph.D.
The Parkinson's Institute
Epidemiological studies continue to show that there is a decreased incidence of Parkinson's disease among smokers. Parkinson's disease, a neurological disorder characterized by very severe movement abnormalities including tremor, rigidity, slowness of movement, as well as memory losses and personality changes, develops because of a degeneration of specific brain areas. It may be nicotine in cigarettes that is responsible for the "protective" effects, which limit Parkinson's disease in smokers. This study identified the specific molecules in the brain (nicotine receptors) that produced compensatory changes such that parts of the brain function are maintained, even when there is nerve cell damage. These results are important because they suggest that drugs targeting the specific receptors may be particularly effective in treating Parkinson's disease.

Structure of CYP2A6: the principal nicotine oxidase (12FT-0185)
Jason Yano, Ph.D.
The Scripps Research Institute
Nicotine is the major chemical component of tobacco products that leads to the establishment and maintenance of addiction. New drugs or vaccines to treat nicotine dependence can only be developed through a detailed understanding of how nicotine acts in the brain. The objective of this project was to identify the structural features of CYP2A6, the enzyme that is responsible for about 80% of nicotine metabolism in the human body and for the activation of harmful tobacco related carcinogens. Blocking the action of this enzyme would diminish the tobacco-related carcinogen load while also reducing the frequency a tobacco dependent individual needs to use tobacco products or nicotine replacement products. The CYP2A6 gene was successfully engineered to produce catalytically active protein that could be purified from a recombinant host in quantities sufficient for x-ray crystallography. X-ray crystallography provides details at the atomic level necessary to build a comprehensive model of how the enzyme functions to degrade nicotine and to suggest designs of specific inhibitors of the enzyme. The data on the crystal structure of CYP2A6 suggested ways to use this enzyme in the design of small molecular chemical inhibitors. The results were published in a leading journal in 2005.

A novel fMRI smoking craving and reward paradigm (12IT-0198)
John R. Monterosso, Ph.D.
University of California, Los Angeles
The primary aim of this IDEA grant was to assess neural activation related to cigarette craving in the context of opportunities to smoke. For the study, abstinent smokers had opportunities to smoke using a specialized device, simultaneous to the acquisition brain images using functional Magnetic Resonance Imaging (fMRI). Prior research indicated that craving to smoke and cue reactivity are heightened when individuals know they will soon smoke. On each trial of this experiment, cigarette smokers (~12 hours abstinent) were shown a 12-sec video clip of smoking cues (e.g., a cigarette being lit). After the clip, subjects were informed that smoke would or would not be available for the next 20 sec but they should try to use self-control to refrain from

smoking if possible. Reports indicated significantly higher craving when smoke was available than when it was not. Furthermore, when smoke was available, significantly greater activity was observed in brain regions previously associated with both craving and inhibitory control, including the dorsal anterior cingulate cortex and supplementary motor area, the right superior and middle frontal gyri, and the right inferior frontal gyrus extending into the insula.

These results demonstrated that the opportunity to smoke increased craving, and further suggested that when individuals refrain from smoking, neural recruitment is observed in brain regions that have previously been associated with inhibitory control. In conclusion, fMRI may be valuable as a means for assessing the effect of therapeutic smoking-cessation interventions including pharmacotherapies.

Regulatory genes of nicotine adaptation in *C.elegans* (12FT-0048)
Suchitra Jagannathan, Ph.D.
University of California, San Diego
This study set out to study the cellular and physiological roles of nicotinic receptors in an animal model (*C. elegans*) which has several advantages in that both its cell lineage and neuronal connectivity are known, thus allowing for studies on every single cell in the live animal. This study identified the accessory proteins that suppress and/or enhance nicotinic receptors' receptivity to nicotine. Calcium imaging in vulval muscles showed that nicotinic receptors in these accessory proteins had an altered response to agonists compared to a control. The observed phenotypes may be a result of failure of receptor clustering at the neuromuscular junction. Further understanding of how various components of the adaptation pathways in *C. elegans,* involving certain receptors and other accessory proteins, participate in processes determining behavior and adaptation should provide a conceptual model for analogous processes in other organisms, particularly humans.

Individual and gender differences in nicotine sensitivity (12FT-0247)
Minjung Park, Ph.D.
University of California, Irvine
Both animal and human studies clearly indicate that females respond differently to nicotine, the psychoactive component of tobacco. The hypothesis that males and females demonstrate differential stress reactivity and differential sensitivity in response to nicotine, was tested in an animal model. This study found that nicotine differentially affects hormonal and behavioral responses in these animals in a gender-specific way. Moreover, it was determined that gender and neonatal handling or a combination of the two, impacted the response to nicotine. There was also a complex interaction between gender and age in response to the reinforcing effect of nicotine. Data from the current study provide evidence as to how differential stress reactivity may be a regulating factor in initiation of tobacco use and progression to nicotine addiction. Furthermore, data from this study will improve understanding of how nicotine addiction may differ by gender. The combined biochemical and behavioral data from this study should provide a conceptual framework to develop more effective tobacco use prevention and interventions in gender-specific and individual-specific ways.

Tobacco Use Prevention and Cessation

Spanish/English Website for Smoking Cessation Trials (10RT-0326H)
Ricardo F. Muñoz, Ph.D.
University of California, San Francisco
The Latino Mental Health Research Program conducted an initial series of four Internet smoking cessation studies in English and Spanish, examining both self-reported 7-day abstinence and mechanisms related to abstinence (e.g., the impact of major depressive episodes, or MDEs, on the likelihood of quitting). Over 4,000 smokers from 74 countries entered the studies. Studies 1 and 2 evaluated a standard smoking cessation guide (the "*Guía*"). Studies 3 and 4 were randomized trials comparing the *Guía* + ITEMs (Individually Timed Educational Messages) to the *Guía* + ITEMs + a mood management course. ITEMs were emails inviting participants back to the site at specific times.

Six-month, self-reported 7-day abstinence rates were 6% in Studies 1 and 2, 10-14% in Study 3, and 20-26% in Study 4 (using missing data = smoking). The *Guía* + ITEMs condition tended to have higher quit rates, which reached significance at 12-month follow-up in Study 3 and 3-month follow-up in Study 4. Smokers with past (but not current) MDEs tended to be the most likely to abstain and those with current MDEs the least likely. This trend reached significance in Studies 1 and 4. Based on this experience, the investigators established an Internet World Health Research Center at UCSF/SFGH.

Hmong smoking prevalence and tobacco uses (10AT-1101)
Vickie D. Krenz,, Ph.D., M.S.P.H., and Pao Fang
California State University, Fresno Foundation and Lao Family Community of Fresno, Inc.
Door-to-door surveys of a random sample of Hmong adults (18 years and older) and youth (17 years and younger) were conducted in eight California cities with the highest populations of Hmong. Census blocks with high concentrations of Hmong residents were identified and residents in every fourth house/apartment were recruited for participation in the project. Questions covered smoking prevalence, demographic variables, acculturation, experience with tobacco customs, tobacco use, locations where Hmong smoke tobacco, and sources of tobacco information. Findings revealed an impressively low rate of tobacco use among Hmong American adults and youth in California. It appears that Hmong American adults and youth possess strong anti-smoking norms. Furthermore, there was a surprising, apparent lack of relationship between markers of acculturation and tobacco use. These findings have significant bearing on the role of acculturation on tobacco use among California's immigrant populations and tobacco prevention efforts. Further study is needed to understand the protective factors in Hmong tobacco use.

Controlled study of withdrawal symptoms in teen smokers (12RT-0141)
Joel D. Killen, Ph.D.
Stanford University School of Medicine
A total of 138 teen smokers from four continuation high schools in the San Francisco Bay Area were screened to yield a study sample of 79 (61 boys and 18 girls). The ethnic distribution of the sample was: 34% White, 9% Asian, 4% Black, 9% multiple ethnicity, 1% Native American Indian, 9% Pacific Islander, and 34% Other. In individual sessions during the first week,

researchers evaluated the development of nicotine withdrawal symptoms with paper-and- pencil instruments, and measured heart rate, blood pressure, and expired-air carbon monoxide (CO) levels, which are elevated in smokers and thus used to verify reports of non-smoking. They were instructed in behavioral strategies for quitting smoking. During the second week , participants were told not to use any nicotine products for 72 hours, and the measurements were repeated.

Surprisingly, and in contrast to findings from the investigators' previous work, teen smokers did not report increases in symptoms during the second week. Heart rate did decrease, as expected, but not significantly. However, level of nicotine dependence, measured during the screening process, was associated with higher levels of craving for cigarettes throughout the study. Specifically, those teens who reported higher scores on a measure of nicotine dependence reported higher levels of craving for cigarettes during both weeks. This result lends support to previous work suggesting that the smoking behavior of adolescents may be influenced by a dependence on nicotine and suggests that it may be important to characterize levels of nicotine dependence among adolescent smokers in the initial phases of treatment planning and to tailor treatment accordingly.

Cambodian research initiative (12BT-2201)
Robert H. Friis, Ph.D., and Him S. Chhim, M.S., M.P.A.
California State University Long Beach and Cambodian Association of America
In this study of 10 focus groups involving 120 Cambodian subjects, smoking patterns differed with respect to gender and age. Males were four times more likely than females to be smokers. Many smokers also were found to have at least one of the following characteristics: unemployed; unmarried; born in Cambodia; immigrated to the U.S. between 1981 and 1989; current incomes of less than $9,999; low levels of education; and live in rented homes.

The focus groups explored factors that led respondents to smoke. One was social influences by which adolescents' role models or peer group interactions have portrayed smoking as an acceptable and desirable practice. Respondents reported that smoking can relieve stress or help them manage boredom. Because smoking repels mosquitoes and leeches among fieldworkers, smoking has been used for these purposes in Cambodia. Finally, cultural traditions play a significant role in influencing smoking behaviors among Cambodians; tobacco is commonly present in such practices as offerings in religious ceremonies and wedding gifts. Respondents reported that appropriate smoking cessation interventions among the Cambodian community would involve behavior change promoted by other family members (especially children) and physicians, as well as changes made in Cambodian cultural practices and beliefs.

Tobacco Control Policy

Segregation analysis of tobacco use in families (7PT-2001-04)
Gary E. Swan, Ph.D.[1]; Neil Benowitz, M.D.[2]; Dorit Carmelli, Ph.D.[3]; Kirk C. Wilhelmsen, M.D., Ph.D.[3]
[1]*SRI International;* [2]*University of California, San Francisco;* [3]*Ernest Gallo Clinic and Research Center*

This Integrated Research Project entailed four studies by scientists at three institutions that examined the extent to which hereditary factors operate alone or in combination with environmental factors to determine whether adolescents are likely to experiment with tobacco or become regular smokers. Data use in this study derived from 763 adolescents, their parents, and their siblings who participated in a longitudinal Smoking in Families study. Smoking history and other measures were used to create classes of nicotine dependence (ND) characteristics, including tobacco use trajectories (smoking patterns over time) and ND factors (combinations of similar ND characteristics). Specialized statistical analyses revealed that a variety of smoking, ND and alcohol use characteristics appeared to run in families (for example, time to first cigarette in the morning, withdrawal symptoms, and four measures of smoking motivation). DNA samples were analyzed in relation to the smoking and ND characteristics, and a potential link was observed between a location on specific chromosomes and tobacco dependence measures. Exploratory analyses were conducted to determine whether differences at other chromosomal regions affected measures of tobacco use, quitting, and smoking motivations. Nine additional chromosomal areas were implicated: three associated with alternative measures of nicotine dependence, two with current or previous tobacco use, two with the process of quitting/relapse, and two with smoking motivations. Association analyses were also conducted involving genes related to the metabolism of nicotine and other biologic pathways, and initial findings showed nominally significant associations between scores on a nicotine dependence measure and two of the genes in these pathways. To date, the investigators have made 18 presentations and written 11 manuscripts. Additional analyses are expected to continue to make unique and important contribution to the understanding of the role of genetics in nicotine dependence.

Environmental tobacco smoke and adult asthma (10RT-0108)
Mark D. Eisner, M.D., M.P.H.
University of California, San Francisco
This study examined the impact of secondhand smoke (SHS) exposure on adult asthmatics in California. During the past decade, the prevalence of adult asthma has increased more than 50% and mortality has approximately doubled. Better understanding of the factors contributing to asthma morbidity and mortality would have important clinical and public health implications. In particular, identifying modifiable environmental factors such as SHS that exacerbate asthma has become a priority. This study found that the majority of adults with asthma were exposed to SHS, with estimates ranging from 60% to 83% depending on the time frame and methodology. The highest level of recent SHS exposure, as measured by personal nicotine badges, was related to greater asthma severity while controlling for sociodemographic factors and previous smoking history. In addition, directly measured SHS exposure appears to be associated with poorer asthma outcomes. The study provides important information establishing the adverse health effects of SHS in adults with asthma. In public health terms, these results provide further impetus for public policies aimed at creating smokefree public places.

Smoking prevention for Asian American college students (10RT-0142)
Mark Myers, Ph.D.
Veterans Medical Research Foundation
This study examined ethnic and gender differences in smoking prevalence and progression, as well as various factors that may increase or decrease an individual's risk for smoking. Significant

increases were found in the overall rate of cigarette use (current smoking and meeting criteria for nicotine dependence) from the initial to follow-up assessment. One of the few differences between Korean Americans and Chinese Americans was that Korean Americans had higher-rates of nicotine dependence at baseline. Males were found to have significantly higher rates of current smoking at baseline and follow-up, and nicotine dependence at follow-up. Furthermore, males were significantly more likely than females to initiate smoking. The knowledge gained from this study will contribute to understanding why young adults of Chinese and Korean heritage start to smoke, why some of them quit and others continue to smoke.

The analysis of California adolescent tobacco use data (10RT-0333)
William J. McCarthy, Ph.D.
University of California, Los Angeles
The overall goal of this study was to identify new behaviors and environmental influences that may influence adolescent tobacco use. The state of California mandates administration of the California Health Kids Survey (CHKS), an omnibus health practices survey, to samples of 7th, 9th and 11th graders in all public school districts. Health practices assessed in the survey include tobacco use, nutrition, physical activity, violence behaviors, illicit drug use and alcohol use. To date, the CHKS has been administered to over one million students, permitting fine-grained analyses of ethnic differences in tobacco use. The sample of students completing the CHKS from 1998 to 2001 is big enough so that reliable conclusions were drawn for less well-known ethnic groups that have not been described in earlier surveys, such as Native Americans, Central Americans, Laotians, Cambodians, Cubans, as well as students with mixed ethnic ancestry. The study presents tobacco use rates among California middle school and high school students at the state-, county-, and school-level. Analyses yielded racial/ethnic differences in student tobacco use onset, beliefs about tobacco, efforts to quit smoking, as well as the conditions associated with continued smoking or with long-term refusal to use tobacco. The study measured the extent to which tobacco use is associated with other health behaviors and attitudes, such as drug use, perceived harm from smoking, food choices, and concerns about weight. These associations were compared across different racial/ethnic groups. For example, a striking feature of six years of smoking trends in students belonging to specific Hispanic subgroups is how the relative smoking rates of the subgroups stayed the same even as all absolute smoking rates declined. Despite these consistent differences among Hispanic subgroups, major predictors of student tobacco use operated similarly within each group. For instance, depressiveness increased more than twofold the risk of smoking in every Hispanic subgroup, even after controlling for school-level indicators of family income and parental education. Similarly, high academic achievement reduced risk of tobacco use by 23% - 31% across all Hispanic subgroups.

Isothiocyanates among African Americans and Caucasians (11IT-0082)
Catherine L. Carpenter, M.P.H., M.D.
University of California at Irvine
Consumption of cruciferous vegetables (e.g., broccoli and brussels sprouts) has been associated with a protective effect for lung cancer and isothiocyanate (ITC) is thought to be responsible. This study measured levels of ITC in the urine of African Americans and Caucasians who participated in a study of lung cancer conducted during the early 1990's. Measuring ITC directly yielded a more accurate indicator of ITC than self-reports of vegetable consumption. African American subjects had a statistically significant lower a geometric mean ITC than Caucasians,

1.261 vs. 2.19. The difference held for current smokers only, 1.165 vs. 2.034. Though these ethnic differences enhance our understanding of lung cancer prevention, further research is required to determine the cause of the differences (e.g., average differences in amount of cruciferous vegetables consumed, genetic differences, metabolic differences, differences in amount of cigarettes smoked, and differences in other potentially important covariates).

The geography of tobacco-related disease in California (11RT-0093)
Robert I. Lipton, Ph.D.
Pacific Institute for Research and Evaluation
This project used Geographic Information System technology to identify the California locales (by zip code) with the greatest concentration of tobacco-related diseases by looking at the prevalence of hospital-admitted tobacco-related disease rates and smoking prevalence. The project also examined the relationship between tobacco-related disease hospital related discharges (for example, lung cancer, COPD, and heart disease) are related to variations in tobacco-related disease prevalence rate, tobacco sales outlet density, and smoking by California zip code. Differences in tobacco-related disease rates across zip codes were estimated to determine the extent to which they varied from expectations in 1993 and 1999. The study identified high levels of COPD in some zip codes, and socio-demographic variables that were significantly related to COPD prevalence, namely low income and percentage of residents over 45 years of age. Applying spatial analyses to tobacco-related disease, smoking prevalence, and tobacco-related discharges will increase public health intervention and prevention efforts in California.

The determinants of college smoking (11DT-0161)
Fan-Ni Hsia
University of Southern California
The goal of the study was to identify the reasons that Asian American college students in California are initiating smoking in order to design evidence-based, relevant and effective prevention programs for this population. Students attached "personal meaning" to smoking, such as "smoking helps me deal with stress" and "I'm curious what it is like." "Socially relevant meaning" was next most important (e.g., "smoking makes me feel comfortable in social situations" and "smoking helps me to fit in"). The data suggested that socially relevant meaning is more important for males. In addition, Asian Americans appear to hold more negative images of and attitudes toward female smokers than male smokers. Whereas, Asian Americans view male smokers as normal and tend to accept them, they view female smokers as "punk girls" or nontraditional (i.e., not ladylike) and as a result accept them less. Results of this study provide a knowledge base to develop state-of-the-art and evidence-based tobacco use prevention programs suited to Asian American college students in California.

Effect of tobacco related policy change on smoking behavior (11RT-0245)
David Burns, M.D.
University of California, San Diego
This research investigated the effect of tobacco-related policy on the smoking behavior of Californians, including smoking cessation, non-compliance to smoke-free work site restrictions, the effect of over-the-counter availability of nicotine replacement therapy, and the effect of cigarette tax increases. The investigators found that an increase in smoking cessation was

associated with changes in public policies, particularly physician advice to quit, restrictions on smoking in the workplace, and tax increases. These effects were seen in all racial and ethnic groups and by those with lower educational attainment. Logistic regression models showed that food service workers were more likely to be smokers and had a greater probability of reporting non-compliance with smoke-free worksite restrictions than non-food service workers. Other analyses showed an increase in smokers' attempts to stop using tobacco after nicotine replacement therapy became available over-the-counter. The also found an increase in quit attempts after the 1999 state tobacco tax increase. Overall, changes in public policy have the potential to reach a large portion of the population and have an impact on cessation efforts for California's demographic subgroups.

Scientific analysis of secondhand smoke by the tobacco industry (12FT-0144)
Suzaynn F. Schick, Ph.D.
University of California, San Francisco
Analysis of published and unpublished internal tobacco industry documents revealed what and when the tobacco industry knew about the dangers of secondhand smoke and sidestream smoke (i.e., the smoke that rises from the tip of a burning cigarette between puffs). They searched: the Minnesota Depository via the American Legacy Foundation Tobacco Documents Library and industry sites; 120,000 pages from UCSF's Guildford Depository selected for relevance to secondhand smoke; and a collection of legal documents from lawsuits against the tobacco companies filed under California Proposition 65. One finding was that, after Hirayama's paper linking exposure to secondhand smoke and lung cancer was published in 1981, the tobacco industry began to study the toxicology and carcinogenicity of sidestream smoke. Philip Morris found that fresh sidestream (<1 min. old) is two to six times more toxic per gram than mainstream smoke and that the gas/vapor phase is responsible for the majority of sensory irritation and damage to the respiratory tract epithelium. Fresh sidestream smoke can cause damage the respiratory epithelium at low levels, and this damage increases with longer exposures. None of these data, along with data from other studies that found the toxicity of sidestream smoke, were published.

The findings of this research materially contributed to the development of the recent American Society of Heating Refrigerating and Air-conditioning Engineers (ASHRAE) position document that the adverse health effects of secondhand smoke cannot be controlled by ventilation, and to the findings of fact in the recent Department of Justice case against Philip Morris.

Tobacco use, home policy, and life events in at-risk women (12FT-0244)
Liza S. Rovniak, Ph.D.
San Diego State University Research Foundation
Low income women often have multiple stressful life events that compromise their ability to participate and achieve successful outcomes in tobacco control programs, such as reducing their children's exposure to secondhand smoke (SHS). In California, low income women use tobacco to a greater extent than more affluent women, and their smoking levels have not declined as much as higher income groups. Little is known about how to measure stressful life events among low income groups, or about the effects of stressful life events on low income women's ability to reduce their tobacco use. Findings from this study suggest that measurement of life stressors in low income women is complex and requires consideration of personal and ecological factors that

may affect the severity, continuity, and frequency of life stressors. They also suggest that tobacco control programs for low income women should focus not only on women's smoking behavior, but also on contextual factors such as job training, providing appropriate mental and medical health care, and assistance in obtaining stable housing.

Environmental tobacco smoke exposure: Latino asthmatic children (12FT-0260)
Nada O. Kassem, Dr.P.H., M.S., R.N.
San Diego State University Research Foundation
Secondhand smoke (SHS) exposure has been shown to increase the number of episodes and severity of asthma attacks in children. Children's SHS exposure takes place mainly in homes so it is not surprising that home smoking restrictions have been shown to reduce health risks. Asthma is one of the most common chronic illnesses among Latino children. Telephone interviews were conducted with 204 Latino families residing in San Diego County with an asthmatic child, 3 to 17 years of age, who lived in a home with at least one smoker. Results show that 42% of families reported that no smoking was allowed in their homes. However, 13.5% reported that special guests were allowed to smoke in the home; 30.6% allowed smoking in certain areas in the home; and 13.5% allowed smoking anywhere in the home. Although 86.5% of families reported having some smoking restrictions in the home, mothers reported that all children were exposed to SHS. SHS exposure diminished when: spouse and friends talked about SHS; smokers believed that SHS is harmful; frequently asked others not to expose children to SHS; knew how much SHS can harm health; and had restrictions on smoking at home. These results can be used in planning culturally-tailored tobacco control interventions.

Smoking and genes as determinants of RA and SLE severity (13KT-0133)
Michelle Freemer, M.D.
University of California, San Francisco
Grant terminated in the first six months because the principal investigator left California.

Cancer

Chemokine-based therapy for lung cancer (10RT-0053)
Sherven Sharma, Ph.D
University of California, Los Angeles
This project explored ways to boost the body's natural immune defenses against lung cancer, focusing on a naturally-occurring protein called secondary lymphoid chemokine (SLC), which attracts immune cells that help fight cancer. SLC delivery to the tumor site boosts the immune response by attracting immune cells that reverse tumor-mediated immune suppression and orchestrate cell-mediated immune responses. Such immunotherapy can completely cure mice with cancer. The investigators used mouse models to determine the mechanisms by which SLC restores immune cell activity. In addition to defining the multiple immunological pathways involved in the therapeutic response, a novel lung cancer therapy was developed by establishing an alternative method to deliver SLC to tumor cells using genetically modified immune cells.

Bispecific molecule therapy of small cell lung cancer (10RT-0064)
Edward D. Ball, M.D.
University of California, San Diego
Small cell lung cancer (SCLC) is an extremely aggressive form of the disease that is caused by smoking. SCLC cells produce short amino acid chain neuropeptides which promote tumor cell growth. This project developed a new immunotherapy for the treatment of SCLC by exploiting the fact that SCLC cells display receptors for these neuropeptides on their surface. The receptors are molecules that consist of a humanized monoclonal antibody for normal white blood cells combined with the relevant neuropeptide sequence that recognizes tumor cells. Because white blood cells are capable of killing cancer cells and because the neuropeptide sequence specifically recognizes its receptor on the tumor cell surface, this ingeniously designed bispecific molecule causes tumor cell destruction. The principal investigator was awarded a U.S. patent for this invention. The studies evaluated the effect of this therapy in combination with chemotherapeutic drugs, investigated its mechanism of action, and delineated optimal conditions for efficacy. These efforts will contribute to the rational design of future clinical trials for this promising treatment.

Novel agents for apoptosis of lung cancer (11RT-0081)
Xiao-Kun Zhang, Ph.D.
Burnham Institute for Medical Research
One of the normal processes that goes awry in cancer cells is apoptosis or orchestrated cell death. Cancer cells elude the normal process of cell death and survive and multiply uncontrollably. One of the pathways by which this occurs is through a protein called TR3, a nuclear receptor, the expression of which is induced by nicotine. When TR3 resides in the nucleus, it functions to promote cancer cell survival. However when it moves from the nucleus to the cytoplasm, it binds to mitochondria and through a series of intermediate steps, results in cell death. This property of TR3 makes it an attractive candidate for the development of therapeutic agents that control or cure cancer by restoring the normal process of cell death to cancer cells. In the course of these studies, a new apoptotic pathway in cancer cells was discovered: when TR3 travels from the nucleus to the cytoplasm, a mitochondrial protein that is normally a protector of cancer cells becomes a cancer cell killer by binding to TR3. The elucidation of this hitherto unknown pathway guided the design of new analogue compounds that mimic the killing effect of the TR3/mitochondrial protein binding. One of these compounds induces extensive apoptosis of cancer cells *in vitro* and in a mouse model and is, furthermore, resistant to enzymatic degradation. These new compounds are excellent prospects for new cancer therapeutics.

Tobacco-altered tissue of the mouth may promote oral cancer (11IT-0138)
Ana Krtolica, Ph.D.
Lawrence Berkeley National Laboratory
Although it is well-known that the use of cigarettes and smokeless tobacco is associated with oral cancer, surprisingly little is known about the mechanism of this malignant transformation. In a novel approach to this question, experiments assessed the effect of tobacco extract on the cells adjacent to the tumor cells, the so-called supporting cells. Supporting cells are known to regulate the growth and behavior of the cells above them. Several intriguing and potentially useful results were obtained: 1) tobacco extract inhibited the growth of cells from supportive tissue; 2) if the exposure to tobacco extract was high enough, this regenerative capacity was

permanently lost; 3) extract-exposed cells stimulated the growth of potential tumor cells; 4) tobacco-treated supportive cells secreted substances that promote tumor invasion; and 5) some of the substances causing these pathogenic events were identified. This research shed new light on oral cancer inception and progression and suggests unique and new potential targets for therapeutic intervention.

Vascular targeting of lung tumors (11RT-0167)
Jan E. Schnitzer, M.D.
Sidney Kimmel Cancer Center
For decades, cancer researchers have been absorbed by the search for a "magic bullet" anti-cancer therapy that would target cancer cells but not surrounding tissue. This project contributed to the development of a very promising approach. The researchers discovered a lung-tumor induced protein, called Annexin A1, that resides only in the caveolae of lung tumor blood vessels. Caveolae are small folds (invaginations) of the endothelial cell membrane that contain proteins and lipids involved in the transport of molecules from inside the vessels to the tissue. Antibodies were generated that selectively recognize and bind to Annexin A1. Such antibodies rapidly and specifically accumulate in tumor cells and, when labeled with radioactive iodine, induce tumor regression. Thus, caveolae can be exploited as a means to deliver antibody into and throughout the tumor. Large-scale proteomic analysis is providing further promising caveolar protein candidates. The results, which were published in *Nature*, one of the most influential scientific journals, show great promise for the development of efficient and specifically-targeted anticancer therapy delivery to tumor cells.

Focal adhesion kinase regulation of Cox-2 in lung cancer (12FT-0122)
Satyajit K. Mitra, Ph.D.
The Scripps Research Institute
This project clarified a functional relationship between focal adhesion kinase (FAK), a protein that integrates cellular signals promoting cell growth and survival, and cyclooxgebase-2 (Cox-2) a protein that is elevated during malignant transformation in lung cancer cells. High Cox-2 levels are associated with poor prognosis in lung cancer patients and decreasing Cox-2 levels reduces the incidence of lung cancer in heavy smokers. Using genetically modified mice, the research found that FAK expression is linked to both tumor development and high Cox-2 levels. FAK-regulated tumor growth was found to be highly dependent on tumor blood vessel formation and FAK was found to promote this process by inducing the secretion of vascular endothelial growth factor. Thus, FAK was found to be an important player in the development of lung cancer.

CSF biomarkers of brain metastases from lung cancer (12IT-0246)
James Rubenstein, M.D., Ph.D.
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Lung cancer victims typically die not from the localized pathology itself, but from metastasis to other sites, particularly the brain. In fact, of the 150,000 new brain metastatic cancers diagnosed yearly, approximately 40,000 originate from lung cancers. Brain cancers can be much better managed clinically if accurate diagnosis is made early, the site of origin of the cancer is known, and the efficacy of treatment can be monitored. To do this, specific biomarkers of brain metastatic cancer are needed. This project undertook the task of identifying biomarkers of lung

cancer brain metastases in cerebrospinal fluid (CSF) samples from lung cancer patients. The investigator used proteomic analysis, a sophisticated and powerful technique that allows for identification of hundreds of expressed proteins in minute biological samples. By comparing CSF samples from lung cancer patients with lung cancer-free control subjects, at least 50 peptides were shown to be reproducibly and differentially expressed in lung cancer patients. Three peptides were identified by mass spectrometry and a quantitative immunoassay for one promising candidate was developed. This research set the stage for the eventual development of specific biomarkers for both metastatic brain carcinoma as well as lung cancer.

Transcription factor modification: A role in lung cancer? (13DT-0065)
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Transcription factors are proteins that control gene expression. Two such transcription factors, c-Jun and c-Fos, respond to cigarette smoke and other stressors in the cells lining the airways. Interestingly c-Jun and C-Fos can either promote or suppress tumor development; how this dual functionality is controlled is not well understood. This dissertation project focused on one candidate control point: the modification of these transcription factors by the addition of sugars. This work necessitated the invention of a new, faster and more sensitive assay to detect sugar modifications in extremely small protein samples isolated from cells. A novel chemical probe was developed that allowed the identification of sugar modifications not only in c-Jun and c-Fos, but also on two other functionally related proteins. The results suggest that sugar modification of transcription factors may play a greater role in gene expression and tumor development than previously thought.

Heart Disease

Molecular origins of ApoB atherogenic lipoproteins (9RT-0227)
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Cigarette smoking causes coronary atherosclerosis leading to heart attack, the most common heart disease. Atherosclerosis involves the deposition of excess cholesterol and its esters, stimulating the formation of a plaque in the coronary artery wall that can lead to narrowing of the lumen (the diameter of the tube carrying the blood to the heart muscle), and subsequently to the rupture of the plaque which stimulates the formation of an intravascular thrombus, thereby blocking blood flow to the heart muscle. Low density lipoproteins (LDL) and their immediate precursors very low density lipoproteins (VLDL), as well as their partially metabolized VLDL remnants, are the sources of the “bad” cholesterol that damages the artery wall. The liver is the only tissue source of this family of lipoprotein particles, and hepatocytes, the major cells of this organ, assemble and secrete these particles into the blood. The study investigated the VLDL assembly mechanisms in the isolated, perfused mouse liver because the mouse is the only mammal in which genetic engineering is routinely successful. The research succeeded in developing a sound physiologic mouse liver re-circulating perfusion procedure and isolated and biochemically characterized putative first-step particles under control wild-type conditions, one drug-treated condition, and one gene knock-out condition. However, the investigators were

unable to confirm the inhibition of the two-step mechanism and found no differences in first-step particles in any condition, even in perfused mouse livers lacking the LDL-receptor.

Triglyceride metabolism: Genetics, smoking and heart disease (12FT-0226)
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The most common form of coronary heart disease (CHD) is atherosclerosis, a condition in which cholesterol accumulates in the arterial wall and causes the arteries to harden and narrow, which in turn increases the risk of a heart attack. Cigarette smoking is a major risk factor for atherosclerosis and high levels of triglyceride are an independent risk factor for CHD. A better understanding of the atherosclerotic process holds the potential to define new treatments to lower plasma lipids and thus reduce the incidence of CHD. Microsomal triglyceride transfer protein (MTP) is important in the assembly of very low density lipoproteins (VLDL), which are increased in hypertriglyceridemia. Overexpression and accumulation of human apolipoprotein (apo) E in transgenic mice cause hypertriglyceridemia, at least in part by stimulating production of VLDL-triglyceride. This project compared the effects of apoE3 and apoE4 and their interactions with MTP on plasma triglyceride levels in transgenic mice that express human MTP (hMTP) in the liver. They assessed the effects of hMTP activity levels on plasma lipids and lipoproteins and on VLDL production. No changes were observed in lipid or lipoprotein metabolism in hMTP mice, either in the initial or alternative models. A third strategy is being pursued using genetic and biochemical analyses to determine the effects of gene interactions between hMTP and human apoE3 or apoE4 on lipid metabolism in transgenic mice. The knowledge gained should help in the design of new ways to prevent and treat high triglyceride levels and cardiovascular disease in smokers and nonsmokers alike.

The role of platelets in atherogenesis in the mouse (13FT-0144)
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Atherosclerosis refers to deposits of cells, fat, and other materials in the blood vessel wall that narrow the vessel and can cause it to clot, stopping blood flow. These deposits or “plaques” are the most common cause of heart attack and some forms of stroke, and ingestion of cigarette smoke is a major risk factor for the development of these plaques. Platelets are small, blood-borne cells whose primary role is to ‘plug’ damaged blood vessels by forming blood clots, thereby preventing bleeding. The goal of this project was to determine the role of platelets in the initiation and progression of atherosclerosis in the whole animal. Specifically, it is thought that platelets bind to a type of white blood cell called monocytes and help these cells attach to and enter the blood vessel wall. A specific research question is whether platelet-deficient mice are more or less prone to atherosclerosis because of differences in protease-activated receptor-4 (PAR4). The blood-clotting enzyme thrombin is the strongest known activator of platelets and is present in atherosclerotic plaques. Because platelets from mice deficient in PAR4 do not respond to thrombin, it was anticipated that PAR4-deficient mice would behave like platelet-deficient mice in these studies. The project was terminated in the first year when the investigator resigned his postodoctoral fellowship to accept a position at another institution.

Lung Disease

Effect of tobacco smoke on leukocyte adhesion (10RT-0171)
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Chronic inflammation caused by exposure to environmental tobacco smoke (ETS) causes chronic obstructive pulmonary disease (COPD), but the mechanisms by which this occurs are not well understood. One key feature of inflammation is the recruitment of inflammatory circulating cells called leukocytes into the extravascular spaces of the lung. This project explored how leukocytes move from inside the blood vessels to lung extravascular spaces under the influence of ETS and nicotine. The project also studied the effect of ETS and nicotine on the movement of immature blood cell progenitors of blood and immune cells from the bone marrow or peripheral blood stream to the sites of inflammation.

The investigator developed a unique model to study the formation of new blood vessels and the movement of leukocytes. Sections of lung from smoke-exposed mice were transplanted into special viewing chambers in donor mice. The cells were then observed using intravital video microscopy, a method for visualizing cell trafficking within living animals. It was found that circulating leukocytes, as well as neutrophils from smoking human donors, displayed increased interaction with cells lining the blood vessels of lungs exposed to ETS or nicotine alone. The investigator also found that continuous exposure to nicotine can cause immature blood cells to behave abnormally in ways that suggest that they also contribute to smoking-induced inflammation. These results contribute to our understanding of smoking-induced inflammation, and thus the future hope that therapeutics can be developed to halt the progression of COPD.

COPD: Oxygen transport and metabolism in skeletal muscle (10KT-0335)
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Patients with chronic obstructive pulmonary disease (COPD) display impaired exercise capacity. Besides contributing to disease morbidity, this impairment confounds physicians' ability to treat these patients since physical therapy is an important component of their treatment. In order to improve treatment outcome, it is important to understand the underlying cause of this impairment. This project investigated muscle physiology in COPD patients in order to determine if COPD results in skeletal muscle dysfunction and, if so, to determine the mechanisms underlying this dysfunction. Using a variety of techniques including two types of magnetic resonance imaging, the investigator analyzed blood flow, O_2 consumption, inspired O_2, and a host of other metabolic parameters in normal and diseased subjects. A small subset of COPD patients were found to have a mechanical insufficiency that was accompanied by a substantial increase in Type II muscle fibers, which differ from other muscle fibers by, among other things, generating energy by anaerobic metabolism and fatiguing easily. These and other experiments conducted as part of this project are important steps in the continuing effort to distinguish metabolic limitations from O_2 supply limitations and thus provide insights into the physiology of O_2 transport and muscle function in health and disease.

Effect of smoke and gender on bronchiolar injury and repair (11RT-0258)
Laura S. Van Winkle, Ph.D.
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Exposure to secondhand smoke increases the risk of developing lung cancer. Women have a higher risk of lung cancer than men at every level of exposure to tobacco smoke. Recent studies suggest that this gender difference in lung cancer susceptibility has a genetic basis, but virtually nothing is known about the biologic components of this disparity. This project used a mouse model to examine differences in cell biology between male and female mouse lungs as well as cellular changes that occur during exposure to secondhand smoke. The hypothesis was that environmental tobacco smoke (ETS) exposure would predispose the lungs of female mice to injury and that the pattern of injury would vary with the stage of the estrus cycle.

The results of this work show that female mice are more susceptible to naphthalene, one of the most abundant chemicals in secondhand smoke. Female mice form more of a toxic naphthalene intermediate in the lung than do males, particularly in the distal lung, a region that is susceptible to carcinogenesis in women. This metabolic process was influenced by estrus cycle stage. Preliminary work suggests that estrogen receptors may be involved. Exposure to ETS increases the expression of the enzyme that metabolizes naphthalene to a toxic intermediate, but only in females. The lung is capable of mounting a protective response to such environmental insults, which is extremely important in normal lung function. Female mice exposed to ETS were found to lack high levels of an enzyme that is critical component of this protection. Finally, a substantive difference in basal gene expression of a protective lung antioxidant enzyme was found between males and females. These experiments resulted in provocative and entirely original findings that shed much-needed light on lung cancer susceptibility in females. The results have potential impact for women who smoke or are exposed to secondhand smoke and set the stage for the development of strategies that can protect sensitive populations.

IRAK-1 and active TGF-β: Counterregulators in emphysema? (12FT-0123)
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Emphysema is believed to result from a prolonged state of inflammation that eventually results in the irreversible destruction of lung tissue. It is clear that smoke causes lung inflammation; however, the pathways involved in the induction and maintenance of emphysema, even after the emphysematous individual quits smoking, are complex and little understood. This research elucidated certain signaling pathways involved in the inflammation response and the activation of enzymes responsible for the lung tissue destruction characteristic of emphysema. The investigator developed a novel lung alveolar cell system consisting of immortalized cells, thus eliminating the need for primary cell cultures, which must be harvested from animals for each experiment. This system obviates the need for excess animals and eliminates the problems of primary cell culture such as contaminating cells and batch variability. Although the investigator did not obtain evidence in support of the hypothesis that a specific signaling intermediate was a critical component of an inflammatory/enzymatic pathway implicated in the development of emphysema, he is currently designing an alternative strategy which will enable him to subject the hypothesis to a more sensitive test. The development of a lung alveolar cell system and co-culture system will be very valuable to the scientific community devoted to the study of the mechanisms underlying emphysema.

Dietary fat and ETS effects on lung epithelial biology (12IT-0191)
Laura S. Van Winkle, Ph.D.
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Among the negative health consequences of high dietary fat is a higher risk of lung cancer and loss of lung function. In an original and unique approach, this study investigated how diet affects the lung's ability to withstand toxins found in environmental tobacco smoke (ETS), exposure to which is known to cause lung cancer. The investigator found evidence to support the hypothesis that a high fat diet enhances the toxicity of SHS in the lung and that the response differs by gender. First, while toxicity following a high fat diet increased in some lung regions, it decreased in others. Second, substantial differences in glutathione levels were found depending on airway location, gender, diet and history of ETS exposure. This observation is significant because glutathione is an important molecule in the body's arsenal of defense against oxidative stress and toxicity. Third, certain portions of the lung were found to contain a potential regulator of the diet-related responses called adiponectin, a hormone that regulates lipid and glucose metabolism and has certain anti-inflammatory properties. These preliminary data will lead to future studies of the mechanisms by which diet and ETS exposure cause lung cancer, asthma, and bronchitis.

Regulation of a novel airway glandular mucin by smoke (13KT-0101)
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Excessive mucus in the airways is characteristic of chronic obstructive pulmonary disease (COPD). It causes airway obstruction which results in increased morbidity and mortality. Mucus consists of mucin glycoproteins that are coded for by mucin genes. The objective of this project was to understand how mucus overproduction is regulated at the genomic level, with the ultimate objective being the development of specific therapies that minimize mucus production. The investigator discovered a novel mucin gene called *MUC-19*, produced by mucin glands, which produces more than 70% of the total airway mucus. The investigator demonstrated a close association between smoke exposure and *MUC-19* gene expression. The genomic elements controlling the activation of this gene were identified as well as the upstream signaling pathway that turns on smoke-induced *MUC-19* gene expression. The investigator is currently identifying inhibitors that would turn off these "switches" and thus alleviate airway obstruction caused by mucus over-production.

Environmental Tobacco Smoke and Effects of Tobacco Use on Reproductive Processes

Deposition of inhaled carcinogens in ETS (10KT-0003)
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The major constituents of environmental tobacco smoke (ETS) are sidestream and mainstream smoke. Particle size distributions have been determined for five of the major carcinogens in sidestream tobacco smoke and four major carcinogens in mainstream tobacco smoke. The goals of this project were to determine the particle sizes of four of the major carcinogens in ETS, to

verify predicted local airflow patterns within airways, and to estimate carcinogen doses for adults and children. To obtain realistic estimates, various daily activity profiles were used to cover all exposure conditions. The research generated risk assessments, including potential carcinogenic doses to children and adults. The results of experimental studies in idealized and replica hollow models of human tracheobronchial airways confirmed theoretical predictions of enhanced deposition at bronchial bifurcations for submicrometer sized particles. This correlates with locations where bronchial cancer has been reported. Dosimetry modeling using the measured particle size distributions of the major carcinogens in sidestream and mainstream tobacco smoke confirmed that children receive higher doses (amount per pound of body weight) than adults at all levels of activity. These results suggest that risk assessement models involving environmental tobacco smoke should focus on children.

Fertility, smoking and early mammalian development (10RT-0239)
Prue Talbot, Ph.D.
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The ultimate aim of this research is to alleviate human reproductive problems caused by smoking, in particular, by studying the effects of cigarette smoke on female reproduction. One specific aim was to identify the toxicants in cigarette smoke that adversely affect female reproduction and to determine their effective doses using the hamster oviduct to assay ciliary beating, oocyte pickup rate, and smooth muscle contraction rate, and using the chick chorioallantoic membrane (CAM) to assay growth and angiogenesis. Using gas chromatography-mass spectrometry (GC-MS), three major groups of chemicals in cigarette smoke were found to be inhibitory. These included derivatives of pyridine, pyrazine and phenol. Many of the chemicals were inhibitory in the oviductal and CAM assays at nanomolar (billionths) and picomolar (trillionths) doses, and several were inhibitory in femtomolar (quadrillionths) doses. Furthermore, many of the inhibitory chemicals were not previously recognized as toxicants at low doses, and some are on the FEMA GRAS list (Flavor and Extract Manufactures Association-Generally Regarded as Safe list) and are added to consumer products including cigarettes. In addition, experiments done using the antioxidants superoxide dismutase, catalase, and mannitol, demonstrated that reactive oxygen species (ROS) in smoke can also impair oviductal functioning when either the oviduct or OCC are pretreated.

The study also examined the concentration of the inhibitory pyridines, pyrazines, phenols and indoles in smoke from various types of cigarettes, including the newly marketed, so-called “harm reduction” cigarettes. These data showed that traditional commercial and harm reduction commercial cigarettes are in general very inhibitory in the three oviductal bioassays and that harm reduction cigarettes, like the traditional brands, retain chemicals that are highly inhibitory in the oocyte pickup and muscle contraction assays. The amount of each chemical studied in the bioassays was determined using GS-MS. All commercial cigarettes had detectable levels of almost all toxicants. The filter in harm reduction cigarettes seemed to reduce levels of some of the toxicants, but the level of reduction was not sufficient to reverse the inhibitory effects of harm reduction cigarette smoke in the oviductal bioassays. This information could be very important to the consumer who is not necessarily getting a safer product with harm reduction cigarettes.

Workshop on ETS doses (13ST-0176)

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A workshop was held on environmental tobacco smoke (ETS) with a focus on aerosol dosimetry. The "Frontiers in Aerosol Dosimetry Research" Conference took place at the Beckman Center of the National Academies in Irvine on October 24-25, 2005. It was attended by approximately 90 scientists, including postgraduate and graduate students, from 12 countries. Fifty-four papers were presented, ranging from basic to applied topics. Advances in aerosol dosimetry were reported by scientists in numerous disciplines, including chemistry, physics, atmospheric science, engineering, mathematics, physiology, toxicology, microbiology, pharmacology, anatomy, risk-assessessment, medicine, veterinary medicine. For inhaled tobacco smoke particles, the traditional concept of dose – mass of an administered substance, sometimes normalized to body weight or surface area – is far too simplistic. The particles in an inhaled aerosol deposit on airway surfaces in complex patterns, or even be exhaled, avoiding deposition altogether. Once deposited, the fates of particles depend on their physiochemical properties, their initial deposition site, and the health status of the subject. Particles and their components may be cleared by mucociliary action, enter tissue fluids (e.g., blood and lymph), distributed throughout the body, or taken up by cells and tissues in the respiratory tract. Aerosol dosimetry covers all of these dynamic events.

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