Annual Report
2001

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from the University of California
to the State of California Legislature
on the progress of the
Tobacco-Related Disease Research Program
established 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 confronted with the ongoing challenges of identifying, funding, and disseminating new and relevant developments in tobacco research. To this end, TRDRP professional staff go to meetings to stay informed about the latest scientific developments and to network with other scientists who are potential applicants or peer reviewers. Additionally, TRDRP staff engage in communication and collaboration with other organizations to disseminate the experiences gained in California and to learn from other state, federal, and national efforts. Some of the emerging trends that underlie the program's research priorities are:

- New, tailored and targeted interventions using both pharmacological and non-pharmacological therapies.
- Increases in the initiation of smoking in the 18-24 year age group and shifts in adult smoking patterns toward occasional "social" smoking patterns.
- Potential greater health hazards associated with menthol cigarette use.
- Potential beneficial effects of nicotine for some ailments (e.g., Parkinson's disease), while at the same time producing degenerative effects on other parts of the brain.
- Greater understanding of the health impacts of secondhand smoke in different environmental settings and on different populations, as well as effective approaches for reducing these health risks.
- Advances in the fields of genomics, proteomics and gene therapy offer new tools to researchers developing novel diagnostic and treatment strategies for tobacco-related diseases.

For the 2001 funding cycle, TRDRP adopted the following six priority areas :

- Biobehavioral and Nicotine Addiction/Treatment Research
- Biological Research
- Effects of Exposure to Secondhand Smoke
- Epidemiological and Surveillance Research
- Policy/Economics Research
- Socio-Behavioral Research on Tobacco Use

In 2001, TRDRP awarded:

- 67 grants
- for $23.4 million
- at 29 California institutions

These awards, which began July 1, 2001, constituted about 25% of the applications reviewed.

INTRODUCTION

The Tobacco-Related Disease Research Program (TRDRP) is confronted with the ongoing challenges of identifying, funding, and disseminating new and relevant developments in tobacco research; the following are just a few of the emerging trends that underlie the program's research priorities. Tobacco use cessation and nicotine addiction treatment programs have recently gained national attention. TRDRP encourages investigators to test the effectiveness of new, tailored and targeted interventions using both pharmacological and non-pharmacological therapies. Surveys continue to show increases in the initiation of smoking in the 18-24 year age group and shifts in adult smoking patterns toward occasional "social" smoking patterns; interventions, cessation programs and health impact analyses that effectively address these behavioral changes are needed. Increasingly, tobacco researchers and members of the tobacco control community are taking note of the greater potential health hazards associated with menthol cigarette use; African American males who disproportionately use menthol cigarettes, also have disproportionately high lung cancer death rates. Studies in this area have lagged for years. Recent neurological research is establishing that nicotine can have beneficial effects for some ailments (e.g., Parkinson's disease), while at the same time producing degenerative effects on other parts of the brain. The increasing emphasis on public protection from environmental tobacco smoke exposure creates a need for greater understanding of the health impacts of secondhand smoke in different environmental settings and on different populations, as well as effective approaches for reducing these health risks. In addition, advances in the fields of genomics, proteomics and gene therapy offer new tools to researchers developing novel diagnostic and treatment strategies for tobacco-related diseases.

TOBACCO-RELATED DISEASE RESEARCH PROGRAM TO DATE

Program Mission and Goals

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

TRDRP strives to meet the needs of program stakeholders including the tobacco control 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.
- Serving as an information resource for tobacco issues

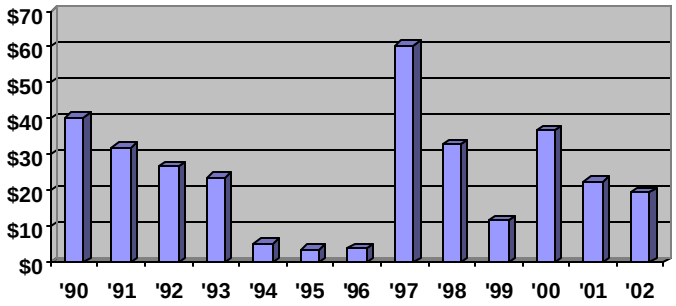
TRDRP strives to meet the needs of the research community by:

- Providing opportunities to researchers to conduct high quality and innovative research that advances tobacco-related science.
- Helping to build the research infrastructure critical for comprehensive tobacco-related disease research.

Funding History

Tobacco sales in California have steadily declined since the Proposition 99 tobacco excise surtax went into effect in 1989. The sole source of TRDRP funds is the Proposition 99 Research Account, which is set by state statutes at 5% of annual surtax revenues. Between 1990-91 and 2000-01, TRDRP resources declined from $26.9 million to $20.2 million annually. Since most of the Research Account funds are appropriated to TRDRP, the program should have shown steadily declining allocations for this period. Instead, the appropriations from the Research Account to the University of California have shown large fluctuations, from a high of $40.3 million in 1990 to a low of $3.65 million in 1995 and back up to $60.4 million in 1997.

Figure 1. Appropriations to TRDRP from Proposition 99 Research Account, 1990 - 2002. ($ in millions)



These fluctuations resulted largely from the fact a substantial portion of the annual revenue was held in reserve for seven years in the early to mid-1900s, pending a policy review by the administration of options for funding other state programs. As a result, TRDRP allocations after 1996 reflected not only annual revenues but allocations from accumulated reserves, creating the continued fluctuations in program funding seen from year to year (Figure 2).

In the past two years, however, TRDRP's funding has again declined, this time due to increased allocations from the Research Account to the California Cancer Registry (CCR). In fiscal years 2000-01 and 2001-02 appropriations to CCR constituted more than 40 percent of its total budget, compared to 10 to 20 percent in previous years.

Award Funding to Date

Since its inception, TRDRP has awarded investigators at 72 California institutions a total of 904 grants for almost $287 million. The grants awarded constitute over 23 percent of the 3764 applications received. The number and dollar amounts funded by Subject Areas are as follows:

Subject Area	***Number***	***Dollars***
Cancer	182	$47,938,215
Cardiovascular Disease	117	$37,114,321
Epidemiology	110	$45,805,576
General Biomedical	97	$25,984,181
Tobacco Use Interventions	95	$42,268,700
Nicotine Dependence	93	$28,299,994
Public Health/Policy	91	$24,679,996
Pulmonary Disease	119	$34,823,290
Total	***904***	***$286,914,273***

Research Involving Women and Communities of Color

Of the 320 currently active grants, 161 (50%) involve humans subjects. Of the 161 human subject studies, 74 (46%) involve women subjects and 73 (45%) involve subjects from communities of color.

2001 FUNDING CYCLE

Research Priorities

The following six priority areas were adopted for the tenth funding cycle:

- Biobehavioral and Nicotine Addiction/Treatment Research
- Biological Research
- Effects of Exposure to Secondhand Smoke
- Epidemiological and Surveillance Research
- Policy/Economics Research
- Socio-Behavioral Research on Tobacco Use

Awards

In 2001, TRDRP awarded 67 grants for approximately $23.4 million to investigators at 29 California institutions. These awards, which began July 1, 2001, constituted about 25% of the applications reviewed. This percentage is quite a bit lower than the 36% in the previous year. Fewer grants will be awarded in 2002 because TRDRP's appropriation for 2001-2002 was only $19.434 million, $3.5 million less than expected.

2001 Award Distribution

Subject Area	***# Awards (%)***	***Dollars (%)***
Health Effects	36 (54)	13,100,794 (56)
Nicotine Dependence	12 (18)	3,312,040 (14)
Interventions/Policy	19 (28)	6,955,923 (30)
Total	67 (100)	23,368,757 (100)

Funding by Award Type	***# Awards (%)***
Research Project	35 (53)
IDEA	5 (7)
CARA/SARA	2 (3)
New Investigator	10 (15)
Postdoctoral Fellowship	10 (15)
Dissertation	5 (7)

Details of all 2001 awards can be found in the TRDRP 2001 Compendium of Awards, which also includes abstracts of all funded projects. The Compendium can be requested from TRDRP 510-987-9870 or trdrp@ucop.edu) or accessed via our website at www.ucop.edu/srphome/trdrp/.

Cornelius Hopper Diversity Award Supplements

The Cornelius Hopper Diversity Supplement Awards (CHDAS) were awarded for the second time. The aim of the CHDAS is to encourage TRDRP-funded principal investigators to mentor

individuals who want to pursue research careers in tobacco use and tobacco-related disease. Qualifications for the CHDAS include recruitment of individuals from underrepresented backgrounds affected by tobacco use or tobacco-related disease, and/or facilitating training of key personnel who will work directly with underrepresented groups that are disproportionately impacted by tobacco use. Seven of our currently funded investigators have received supplements to their TRDRP grants for support of new personnel on their projects.

CHDAS Trainee	*Principal Investigator*	*Institution*
Tina Griffith	Richard Olmstead	University of California, Los Angeles
LaTasha Mason	Bruce Allen	Charles R. Drew University of Medicine & Scienc
Thang-Giao Nguyen	Tanima Gudi	University of California, San Diego
Theresa Operana	John Cashman	Human BioMolecular Research Institute
Michael Romney	Connie Pechmann	University of California, Irvine
Darya Soto	George Caughey	University of California, San Francisco
Frederick Zamora	James Tucker	Lawrence Livermore National Laboratory

2001 TRDRP ACTIVITIES

Information Dissemination

In accordance with its legislative mandate, the University of California continues to actively disseminate the findings of TRDRP-sponsored research. The knowledge gained from TRDRP-funded studies, when applied to tobacco control programs supported by the Proposition 99 Health Education Account, are helping to maximize the effectiveness of these efforts.

Publications

TRDRP-funded investigators have also continued to actively disseminate findings from their research at scientific conferences as well as in scholarly publications. Among the 159 citations were 51 published articles, plus an additional 21 articles "in press" (i.e., accepted for publication and awaiting appearance in print). These publications appeared in such premier scientific journals as the *Journal of the American Medical Association, Proceedings of the National Academy of Sciences, Journal of Biological Chemistry, Cancer Research, Journal of Clinical Investigation, Circulation, Journal of Immunology, Neuroscience, Nicotine and Tobacco Research, Tobacco Control, Journal of Pediatrics, and American Journal of Pathology.*

Annual Investigator Meeting (AIM 2000)

On November 30 – December 1, 2000, TRDRP convened its fifth Annual Investigator Meeting (AIM 2000) with the theme, **Environmental Tobacco Smoke: Dying Without Trying?.** Over 425 registered, a record number. The Western States Affiliate of the American Heart Association, the American Cancer Society – California Division, the Tobacco Control Section of California's Department of Health Services, and a number of TRDRP-funded neuroscientists held a series of very successful and well-attended workshops on November 30. The conference continued on the second day with a plenary session addressing the biology, epidemiology, and policy aspects of ETS. In scientific poster sessions, TRDRP-funded investigators presented their latest findings on many tobacco use issues, including cancer, heart disease, prevention, lung disease, nicotine dependence, policy research, epidemiological studies, health effects on women and infants, and secondhand smoke exposure.

The sixth Annual Investigator Meeting (AIM 2001) took place on December 6-7, 2001 in Los Angeles. The theme for the conference was **Racial and Ethnic Disparities in Tobacco-Related Research**. Due to the timing of the conference it is not possible to report on the outcome at this time; a meeting summary will be part of the 2002 annual report.

Outreach

Newsletter

TRDRP publishes a newsletter three times per year: in March, July, and November. Each newsletter features articles on critical issues in tobacco-related disease and tobacco use, along with information about the program and notices of upcoming events. These are posted on the program's website and approximately 3000 copies are mailed to program stakeholders.

Website

TRDRP has a website at www.ucop.edu/srphome/trdrp where all program publications and announcements can be found for easy access by potential applicants as well as other stakeholders.

CARA/SARA Workshops

TRDRP continued its support of the CARA (Community-Academic Research Award) and SARA (School-Academic Research Award) mechanisms by holding a series of three day-long workshops in Oakland, Los Angeles, and San Diego during October in collaboration with the California Department of Education – Healthy Kids Office. The sessions were aimed at explaining the theoretical approaches to community research and outlining TRDRP's evaluation criteria of these proposals. Response to these workshops was tremendous, with over 100 registrants at the three sites. From the comments of the participants it was clear that this type of outreach was well received.

Conferences

TRDRP Director Hildebrand-Zanki gave a talk on the California experience with smoke-free workplaces, in part using research data generated by TRDRP-funded investigators, at the European Conference "Smoke Free Workplaces", Berlin, May 10-11, 2001. Research Administrator Gardiner was a panelist at the meeting of the Intercultural Cancer Council in Washington, DC. He and his colleague, Francisco Buchting, participated in the Tobacco Control Conference Project Directors' Meeting, Squaw Creek, November 5-8, 2001 to promote collaborative research opportunities between academic researchers and tobacco control professionals. Dr. Gardiner also was a panelist at the National Tobacco Control Conferences in New Orleans, LA, November 26-30, 2001. At this conference, TRDRP teamed up with the California Tobacco Control Section to host a booth in the exhibitor's area.

Site Visits/Information Meetings

During the year, the TRDRP research administrators have conducted site visits and information meetings at institutions receiving funds from TRDRP. These meetings served to inform funded and potential investigators about emerging issues in tobacco research, TRDRP's research priorities, and the application process.

Other Activities

TRDRP actively participates in state tobacco control activities. Director Hildebrand-Zanki is this year's chair of the Next Generation Alliance for Tobacco Control (NGA). NGA is funded by a Smokeless States Grant from the Robert Wood Johnson Foundation to reduce tobacco use through statewide implementation of an evidence-based model smoking cessation program throughout California's managed care delivery system. In addition, Director Hildebrand-Zanki was appointed by the governor to the Tobacco Education and Research Oversight Committee.

At the national level, TRDRP engages in communication and collaboration with other organizations to disseminate the experiences gained in California and to learn from other state, federal, and national efforts. Director Hildebrand-Zanki is the current co-chair of the National Organization of Tobacco Use Research Funders (NOTURF). She also chairs the Research Advisory Committee for the Minnesota Partnership Action Against Tobacco (MPAAT) and the Tobacco Control Research Panel for the Louisiana Health Excellence Fund. TRDRP has played a critical role in launching the Colorado Tobacco Research Program (CTRP). The legislation for CTRP modeled after the TRDRP enabling legislation and the program began operations in 2000. CTRP has contracted with TRDRP to conduct the peer review of CTRP applications, in order to take advantage of TRDRP's extensive experience in conducting peer review for a wide range of tobacco-related research.

TRDRP professional staff are members of a variety of relevant professional organizations. They go to meetings to stay informed about the latest scientific developments and to network with other scientists who are potential applicants or peer reviewers.

2002 FUNDING CYCLE

Budget for 2001-2002

The appropriation for TRDRP from the Proposition 99 Research Account for the 2001-02 fiscal year is $19.434 million. For the second year in a row, the DHS Cancer Registry received an allocation that is $3.2 million above the usual $1.7 million appropriated from the Research Account for a total of $4.930 million. As smoking rates continue to decrease over the next few years, all Proposition 99-funded programs, including TRDRP, will need to adapt to reduced revenues. However, the redirection of already diminishing funds is having a detrimental effect on the program's ability to achieve its goals.

Research Priorities

The Call for Applications and Application Packets for the 11th annual grant cycle in 2001-2002 were issued in September 2001. The submission deadline for new applications is January 17, 2002, with funding for new awards slated to begin on July 1, 2002. The research priorities for this cycle are:

Biobehavioral and Nicotine Addiction/Treatment Research

TRDRP is seeking to fund basic biobehavioral investigations of the biological, psychological, sociocultural, and genetic factors that influence initiation of tobacco use, progression to nicotine addiction, smoking cessation, and relapse; the pharmacological basis of nicotine addiction, including, but not limited to, the role of nicotine receptors and nutrition; the appropriate role of

nicotine replacement therapies (NRT) in nicotine addiction; research that identifies, tests, and disseminates interventions to treat addicted tobacco users; studies that shed light on how nicotine addiction may differ by gender, race, and age; the impact of menthol on addiction and disease development; explorations of applying the "harm-reduction" paradigm to tobacco use; and studies of the potentially beneficial effects of nicotine for the prevention or treatment of disorders such as Parkinson's disease.

Biological Research

TRDRP seeks studies that strive to reduce the morbidity and mortality from tobacco-related diseases. Appropriate areas include basic disciplines – such as physiology, cellular biology, or pathology – as well as translational, applied, and clinical investigations that focus on problems associated with tobacco use. TRDRP encourages studies that identify and validate biomarkers of tobacco exposure and tobacco-induced cellular events relating to the different stages of disease progression; improve the early detection and treatment of tobacco-related diseases; develop novel treatments; examine the mechanisms by which tobacco use contributes to disease progression and management; the effects of prenatal and postnatal exposure to parental tobacco use; and studies that contribute to the understanding of the effects of smoking on human health and how these effects may differ by age, ethnicity, race or gender.

Effects of Exposure to Environmental Tobacco Smoke

TRDRP is seeking to fund research that focuses on the biomedical impact of exposure to environmental tobacco smoke (ETS). In addition to research on chronic ailments directly associated with tobacco smoke exposure (e.g., atherosclerosis), studies into the mechanisms, diagnosis or treatment of pulmonary diseases associated with childhood exposure to secondhand smoke (e.g., chronic bronchitis) or exacerbated by ETS (e.g., asthma) are encouraged. Important in this regard are quantifying and understanding the effects of chronic exposure to secondhand smoke; how the impact of exposure to secondhand smoke differs by age and by other demographic factors, emphasizing the need for appropriately designed studies to characterize potentially disproportionate exposures and sensitivities.

Epidemiological and Surveillance Research

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

Policy/Economic Research

TRDRP is especially interested in funding evaluative research that examines the impact of state and local public policies and programs on smoking rates and practices. Included are studies of regulatory policies of governmental, nonprofit, and for-profit organizations that limit or

discourage access to tobacco products; studies which look at the policy implications for FDA jurisdiction over nicotine and how safety claims for new products developed by the tobacco industry will be evaluated; research into health care policies and the medical sector's actual and potential role in reducing tobacco use in California; studies on the impact of social norm change interventions on tobacco use; evaluation of efforts to eliminate the tobacco industry's promotions of tobacco products. TRDRP also encourages research that documents the role of anti- and pro-tobacco forces in shaping California tobacco policies (e.g., smoke-free bar issues); assesses the impact of the Master-Settlement Agreement (MSA) on state and local anti-smoking policies; and elucidates new strategies employed by the tobacco industry to maintain its lobbying influence; research that illuminates the economic impact of tobacco control policies and their differential effect on California's diverse populations, and that will further enhance the effectiveness of the California Tobacco Control Program.

Social/Behavioral Research on Tobacco Use

TRDRP seeks basic and applied social/behavioral research in the prevention of tobacco use. Topics may include, but are not restricted to, tobacco use in schools and communities; experimentation and the casual use of nicotine products; or exposure to secondhand smoke. Interventions in historically understudied communities or specific racial and ethnic groups to elucidate unique factors and forces shaping their cigarette consumption are invited. TRDRP encourages studies that illuminate the role of acculturation among Latinos, Asians/Pacific Islanders and other immigrants; the resiliency among African American youth compared to the historically high rates of smoking among white and Native American youth; and document trends and develop interventions to curb the rise in smoking among young women.

Award Funding

Award Mechanisms

Investigator-initiated Research

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

Innovation in Research

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

Research Training

TRDRP offers three awards types that are aimed at enhancing the scientific infrastructure for tobacco-related research in California. **New Investigator Awards** are aimed at steering newly independent investigators towards 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

The **Community-Academic Research Award (CARA)** is intended to stimulate and support collaborations between community-based organizations and investigators to perform scientifically rigorous research into tobacco control issues important to California's diverse communities. The **School-Academic Research Award (SARA)** is jointly funded by the California Department of Education (CDE) and TRDRP. The purpose of the SARA is to stimulate and support collaborations between schools and academic 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 sensitive, and appropriate in terms defined and accepted by the schools.

Evaluation Procedures

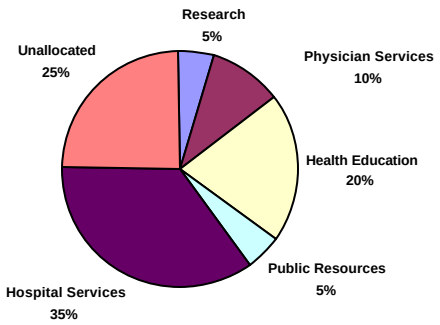
Applications submitted in response to TRDRP's Call for Applications are assigned to a study section comprised of expert reviewers from outside California appropriate for the scientific discipline and subject matter of the proposed research. Out-of-state reviewers are used to minimize potential conflicts of interest. Each study section evaluates applications on scientific merit. The evaluation procedure is modeled on the one used by the National Institutes of Health (NIH). The study sections' merit ratings for each proposal are transmitted to the Scientific Advisory Committee (SAC) which uses them as the primary basis for funding recommendations. The awards recommended for funding by the SAC represent important and innovative research that promises to advance knowledge needed to effect meaningful tobacco control, tobacco use prevention and cessation, protection from secondhand smoke, and prevention, treatment, and diagnosis of tobacco-related diseases.

TRDRP BACKGROUND

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 separate accounts in which specific percentages of the revenue were to be deposited (see Figure 2): the Research Account (5 percent), the Educational Account (20 percent), the Hospital Services Account (35 percent), the Physician Services Account (10 percent), the Public Resources Account (5 percent), and the Unallocated Account (25 percent). Collection of the tax began on January 1, 1989.

Figure 2. Distribution of Tobacco Tax Revenue as Specified by Proposition 99



Proposition 99 specified that the revenues from the Research Account be used to fund research on tobacco-related disease in California. The California State 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 derived 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 part of the Special Research Programs (SRP).

Scientific Advisory Committee (SAC)

In accordance with enabling legislation, a Scientific Advisory Committee (SAC) advises the University on the direction of the research program. Current SAC members represent major California organizations involved in health research. Members are appointed to three-year terms without compensation, and may not receive TRDRP funding while serving on the Committee. The SAC 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 panels.

TRDRP Coordination with Proposition 99 Health Education Account Programs

TRDRP administers the Proposition 99 Research Account. The Tobacco Control Section (TCS) of the California Department of Health Services (DHS) and the California Department of Education (CDE) jointly administer the Proposition 99 Health Education Account. During 2000, TRDRP staff worked with their TCS and CDE counterparts, in order to keep abreast of developments in their respective programs, avoid duplication of effort, benefit from exchanging available expertise, and provide input into the development of each program's goals. To this end, TRDRP conducted a workshop about the CARA award mechanism at the TCS Project Director Meeting. The joint funding of SARA awards between CDE and TRDRP marks the first time that state-level agencies are pooling their resources to optimize tobacco control efforts of common interest. The University has appointed representatives from both DHS and CDE to the TRDRP Scientific Advisory Committee in order to facilitate coordination between the State's research and community- and school-based tobacco control efforts.

RESULTS OF FUNDED RESEARCH

The results of some of the research projects that ended in 2001are summarized below. The information presented here was taken from the final progress reports submitted by the principal investigators.

Health Effects of Tobacco Use

In order to understand how cigarette smoke causes lung cancer, it is necessary to understand the molecular mechanisms of DNA damage cause by cigarette smoke components. If this damage is not repaired efficiently it can eventually cause gene mutations. **Gerd Pfeifer, Ph.D.,** at the **Beckman Research Institute of the City of Hope, Duarte** measured DNA adducts induced in genes frequently associated with lung cancer by several the cigarette smoke carcinogens. He found that the combined DNA damage distribution patterns matched well with the occurrences of mutational hotspots in the p53 gene from smokers, but not nonsmokers. This work increases our understanding of the mechanisms of cancer causation by cigarette smoke. His findings have been employed in science-based tobacco use prevention efforts by the government of Australia (see http://www.quitnow.info.au/damage.html#anchorp53).

Another mechanism involved in the development of cancer in smokers was elucidated by **Xiao-kun Zhang, Ph.D.,** of **The Burnham Institute, La Jolla**. Dr. Zhang found that nicotine causes cancer cell growth by interfering with the inhibitory effects of vitamin A. His data convincingly demonstrated the mechanism of nicotine action in cancer cells and possibilities of suppressing nicotine effects. His studies also revealed a class of nicotine compounds that may be effective against tobacco-associated diseases.

Airway inflammation is an important etiological factor for tobacco smoke induced chronic obstructive pulmonary disease. At a cellular level, lung inflammation is characterized by the recruitment of circulating leukocytes into extravascular spaces of the lung. **Pragada Sriramarao, Ph.D.,** of the **La Jolla Institute for Molecular Medicine** has been able to visualize how circulating leukocytes traffic through lung microvessels and respond to stimuli such as nicotine. Their data show that nicotine plays a pro-inflammatory role in causing increased leukocyte adhesion and retention in lung microvessels. Dr. Sriramarao also demonstrated that exposure to nicotine or tobacco smoke results in the inhibition of bone marrow red blood cell production.

Bruce Ames, Ph.D., at the **University of California, Berkeley** conducted a study to examine, among other variables, the interaction of smoking and diet. He discovered that, when the diet of smokers is equal to the diet of nonsmokers, the only circulating antioxidant that is depleted is vitamin C. This finding was used by the national Academy of Sciences to justify setting a separate requirement for vitamin C for smokers. Dr. Ames also showed that folic acid metabolism is impaired in men who smoke. This could be due to an inactivation of vitamin B12 by the nitric oxide in cigarette smoke. Vitamin B12 deficiency causes chromosome breaks in humans. Dr. Ames' team also showed that low folic acid in seminal fluid is associated with low sperm count and quality in both smokers and nonsmokers.

In a long-term study that already has shed light on the interaction of smoking, reduced fertility, and increased incidence of ectopic pregnancies, **Prudence Talbot, Ph.D.,** of the **University of California, Riverside** has found that some members of a major group of chemicals found in cigarette smoke, pyridine derivatives, impaired oviductal functioning and angiogenesis (formation of new blood vessels) at very low concentrations. At least one of these chemicals is added to cigarettes as well as food and cosmetic products. These findings appear to be highly significant and may provide important public health information on a chemical generally regarded as safe but which inhibits several biological processes at picomolar doses.

In a study on a related topic, **Gayle Windham, Ph.D.**, of the **Sequoia Foundation, Oakland** examined the effects of tobacco smoke exposure on hormones and fertility. Dr. Windham found that changes in hormone function from smoke exposure could impact not only a woman's ability to have children, but other significant aspects of her health as well, such as menopause and development of hormone-dependent cancers.

Disease Progression

Hrayr Karagueuzian, Ph.D. of the **Cedars-Sinai Medical Center, Los Angeles** conducted a study to determine the vulnerability of diseased heart ventricles to nicotine in promoting rapid and disorganized rhythms (ventricular fibrillation, VF) that are incompatible with life. He and his team discovered that nicotine, at concentrations found in the blood of smokers, led to a complete loss of regular activation patterns and to very rapid and irregular activity that signaled the onset of VF. The effect of nicotine was most apparent in the diseased area of the ventricle compared to adjoining normal non-diseased areas. These results provide mechanistic insight into nicotine's profibrillatory influence on the disease ventricle and indicate that the use of nicotine and nicotine products in patients with chronic myocardial infarction carries a high risk of sudden cardia death caused by VF. Dr. Karagueuzian suggests that nicotine not be used in such high risk patients and that in such patients increase in heart rate carries a particularly ominous outcome. Additionally, it appears that nicotine use in patients with myocardial infarction may also be accompanied by greater incidence of failed defibrillation shocks.

Early Detection

Cancers of the head and neck account for about 1.5% of all cancer deaths. Studies have shown that non-drinking smokers have a 4- to 13-fold increase in risk for this cancer. Magnetic Resonance Imaging (MRI) is currently the key clinical tool for deciding between surgery and chemotherapy treatment. **Albert Macovski, Ph.D.** of **Stanford University** has developed a Prepolarized MRI (PMRI) that can reduce the cost of making this decision, as well as the cost of treatment staging. Ultimately, he hopes that a PMRI scanner could be inexpensive enough that society could justify screening high-risk patients. Screening is now routine for diagnosing colon cancer, and early diagnosis is the best predictor of survival. Hence, PMRI could improve the survival rate and reduce the total societal costs of treating tobacco-related tumors of the head and neck.

Treatment

Gladys Block, Ph.D., of the **University of California, Berkeley,** looked at the effect of antioxidants, such as vitamin E and C, on reducing free radical damage. Her study results show that vitamin C reduces one of the makers of oxidative damage, which indicates a potential mechanism by which vitamin C plays a role in the prevention of smoking-related diseases. The study also showed that exposure to secondhand smoke as little as one cigarette a day indoors lowers the body's antioxidant level and therefore lowers the body's ability to prevent oxidative damage.

In related work, **Marcia Dawson, Ph.D.,** of the **Molecular Medicine Research Institute, Sunnyvale** found that a derivative of vitamin A inhibits the growth and induces programmed cell death of lung cancer cells. Dr. Dawson has synthesized novel related agents in an attempt to use rational drug design to the identification and development of therapeutic agents for the treatment and prevention of lung cancer.

Erkki Ruoslahti, M.D., Ph.D., of **The Burnham Institute, La Jolla** has developed a novel way to design targeted anti-cancer compounds that are easier to make than earlier targeted drugs. The principle is to use a peptide (a short piece of protein) that enters the cell and causes its death. Dr. Ruoslahti is currently working on optimizing the killer peptide component to reduce its non-selective toxicity and then test the new compounds for their efficacy in lung cancer models.

Steven Dubinett, M.D. of the **University of California, Los Angeles** conducted an innovative study to boost the immune system against lung cancer by using specialized immune enhancing cells call dendritic cells. This type of therapy is able to completely cure mice with cancer. In order to develop dendritic cell immunotherapy for human patients with lung cancer, Dr. Dubinett focused on determining how this therapy works in mice. He found that dendritic cells injected into the tumor move to lymph nodes where they stimulate white blood cells to kill tumor cells. The movement of dendritic cells to lymph nodes may be a critical determinant of the immune system's capacity to recognize and kill tumor cells at sites distant from the primary tumor. These distant tumor sites, called metastases, are difficult to treat by conventional therapies and are a major cause of death in lung cancer patients. Dr. Dubinett and his team are continuing this line of work to make this immune enhancing therapy even more effective and to begin testing this therapy in humans.

David Dichek, M.D., of the **J. David Gladstone Institutes**, **San Francisco** is working on gene therapy for tobacco-related vascular disease. He and his team have identified two proteins that may be involved in regulating the pathways by which smokers develop tobacco-related disease in the blood vessel wall. Clarification of these pathways may lead to the development of gene therapy or drug therapy approaches that improves the success of therapeutic vascular procedures in smokers and thereby reduce morbidity and health care expenditures.

In a project aimed to improve the effectiveness of treatment for people with lung disease produced by cigarette smoking, **Richard Casaburi, M.D., Ph.D.** of the **Harbor-UCLA Research and Educational Institute** found that both strength training and testosterone supplementation will be beneficial additions to programs of pulmonary rehabilitation for patients

with chronic obstructive pulmonary disease and, thereby, help decrease the suffering of patients with this smoking-related disease.

Social/Behavioral Research

In a study looking at tobacco use and cessation among drug users, **Yih-Ing Hser, Ph.D.,** of the **University of California, Los Angeles** found the greater a respondent's tobacco use, the greater was his/her likelihood of reporting a current disability. Change in smoking status was found to be associated with subsequent improvements in general health and vitality. There was also a positive relationship between tobacco use and illicit drug use as reflected in positive urine tests. Long-term abstinence from tobacco was associated with desirable indices of physical and emotional health but short-term abstinence obtained during drug abuse treatment was associated with increased psychiatric and employment-related problems.

Scott Carvajal, **Ph.D., M.P.H.,** of **ETR Associates, Santa Cruz** looked to identify global determinants of tobacco use onset in diverse youth. He found that parental relatedness in White teens and optimism in low socio-economic status teens appear to be critical predictors of risk for smoking, and should be considered as targets for smoking prevention programs that begin earlier than the traditional programs focused on middle school-aged students. He also found that Latinos who are attached to and functional with their own culture as well as with other cultures appear to have lower levels of risk factors for future smoking.

Studies that have targeted Southeast Asians have focused primarily on Cambodian, Laotian, and Vietnamese. However, there are no studies that estimate smoking prevalence among the Hmong, nor research that explores the tobacco use of this unique group. **Vickie Krenz, Ph.D., M.P.H.,** of the **California State University, Fresno** conducted a pilot study that led to a preliminary understanding of the tobacco-related patterns and cultural practices of the Hmong. She also developed an initial survey instrument to further assess smoking and tobacco use among a cultural group for which a paucity of research exists. Dr. Krenz is currently funded by TRDRP under the Community-Academic Research Award mechanism to extend her studies in this population.

Fen Rhodes, Ph.D. of the **California State University, Long Beach** looked at cigar smoking among young adults. He found that African-Americans appear to be the most vulnerable population for regular cigar use, and particular emphasis should be placed on this group for preventive efforts focused on encouraging the cessation of regular cigar use. In addition, the strong association between cigar experimentation and regular cigarette smoking highlights the importance of efforts aimed at prevention tobacco use in general among young adults. Efforts aimed at encouraging cigar makers to adhere to the same marketing code utilized by cigarette makers, in which the use of sex and celebrity is forbidden, may help to reduce cigar use among young adults.

Mary Ann Pentz, Ph.D. of the **University of Southern California** examined whether school tobacco policy could be improved to help decrease smoking among youth. She developed and evaluated a tobacco policy intervention to enhance the effects of school policy on youth smoking. The major mediators of change in tobacco use were changes in perceived social norms

for tobacco use and the support for the policy. Although there were few ethnic differences, Latino students showed the highest pro-smoking environment and Asian students the lowest.

Nicotine Dependence and Smoking Cessation

Katumi Sumikawa, Ph.D., of the **University of California, Irvine** has conducted a study to see whether the action of nicotine on nicotine receptors in the hippocampus, a structure in the brain involved in learning and memory, is one likely mechanism underlying the cognitive enhancement effects of nicotine. His studies in rats have shown that acute and chronic nicotine exposure inactivate one type of nicotine receptor and persistently activate the other type of nicotine receptor in the hippocampus. Both of these nicotine actions strengthen the connections between the principal neurons present there. The strengthening of the connections has been suggested to be particularly important for learning and memory. Thus, this effect of nicotine may represent the cellular basis of nicotine-mediated cognitive enhancement, which may produce a positive feeling, contributing to nicotine-seeking behavior. Dr. Sumikawa also found evidence that nicotine withdrawal adversely impacted the functioning of the hippocampus.

Research studies show that pharmacists are effective in helping patients quit smoking yet few pharmacists have received formal training for providing tobacco cessation counseling. **Karen Hudmon, Dr.P.H., R.Ph.** of the **University of California, San Francisco** and **Marilyn Shreve, R.Ph.** of **SRI International, Palo Alto** conducted a project to develop and strengthen partnerships between the pharmacy community and tobacco researchers. Tobacco cessation training programs were implemented and evaluated to increase their effectiveness for California's pharmacists as well as other health professional students.

Effective, economical, targeted smoking cessation and relapse prevention programs that reach millions of hospitalized American smokers each year have the potential to decrease the burden of disease, disability, and death resulting from tobacco use. **Joel Simon, M.D., M.P.H.**, of the **University of California, San Francisco/San Francisco VA Medical Center** found that hospital-based intensive counseling and follow-up plus the nicotine patch is more effective than hospital-based minimal counseling plus the nicotine patch in increasing 6-month and one-year quit rates. Because hospitalization presents a unique window of opportunity to reach smokers who may want to quit, Dr. Simon and his team believe that the necessary resources should be found to fund clinically-proven intensive hospital-based smoking cessation interventions.

Environmental Tobacco Smoke

A study of the effect of sidestream smoke on lung injury and repair by **Laura Van Winkle, Ph.D.** of the **University of California, Davis** found that exposure to environmental tobacco smoke (ETS) concurrently with another toxic agent (many of which are present in our daily environment as air pollution) results in an inability of the lung to repair. Another key finding is that chronic exposure during lung development and lung injury may affect females differently than males. These results are relevant to two sensitive subpopulations, women and children.

Lisa Miller, Ph.D., of the **University of California, Davis** examined the effect of ETS on T-cell recruitment in the lung. She found that in a rodent model exposure to ETS for three weeks

resulted in an overall increase in lymphocytes and dendritic cells within airways. These results identified one potential mechanism by which inhalation of ETS may promote chronic inflammation within the lung. Dr. Miller also found that exposure of the airways to volatile components of ETS result in the enhanced expression of chemokines in the lung. Chemokines specifically bring inflammatory cells into the lung. These findings suggest another potential mechanism by which persistent inhalation of secondhand smoke can result in airway inflammation and chronic lung disease.

Also at the **University of California, Davis, John Rutledge, M.D.,** has shown unequivocally that environmental tobacco smoke injures the endothelium in artery walls and increases the endothelial permeability. Antioxidants did not appear to prevent any of the vascular toxic effects of ETS. Data from Dr. Rutledge's lab indicate that certain aldehydes present in ETS may be the leading culprits as far as determining vascular disease as a result of tobacco smoking.

Paul Switzer, Ph.D. of **Stanford University** has developed a computer model to quantify population exposure to secondhand smoke. This model predicted that an appreciable percentage of Californians living in homes with smokers would experience exposures that exceed the annual average EPA health-based standard for fine particles, while ETS fine particle exposure would not often exceed the 24-hour standards. Dr. Switzer's model also demonstrated the important role of ETS exposure in vehicles, an issue that requires further study.

A study looking at indoor measurements of ETS by **Richard Sextro, Ph.D.,** of the **Lawrence Berkeley National Laboratory** showed that the use of nicotine is problematic with respect to accuracy as a marker for ETS exposure. In the smoking areas of homes, nicotine appeared to be a suitable indicator; however, in the non-smoking regions, nicotine behavior was very inconsistent. Other traces, such as ultraviolet-absorbing particulate matter and fluorescent particulate matter, provided a better basis for estimating ETS exposure in the 'real world'. The use of solanesol was compromised by exposure to light during collection.

Tobacco Control Policy

A study by **Lisa Bero, Ph.D.** of the **University of California, San Francisco** examined the role of research in the formation of tobacco control policy. Dr. Bero found that discussions of health effects and economic research play a substantive role in smoking restriction regulatory policy development. Among other findings, Dr. Bero's data suggest that the tobacco industry attempts to shift the arguments about regulation from the health effects of passive smoking to the possible economic effects of smoking restrictions. The public health community can keep the debate focused on the adverse health effects of passive smoking by citing the strong body of literature in this area. It also appears, that the tobacco industry has less influence at the regulatory than at the legislative level.

Helen Schauffler, Ph.D. of the **University of California, Berkeley** conducted the first statewide assessment of smoking control policies in health maintenance organizations (HMOs) in the United States to estimate the prevalence of smoking control policies among the 95 HMOs licensed and operating in California under the Knox-Keene Act. Her findings suggest that the majority of smokers in California HMOs are not covered for the tobacco dependence treatment services that have been demonstrated to be most effective in helping them quit smoking.

In addition, she found that few HMOs were offering support services recommended in the U.S. Public Health Services Clinical Practice Guidelines for Smoking Cessation, nor were purchasers requesting coverage of these benefits. She concludes that a great deal more work needs to be done with purchasers, health plans, and providers to increase the provision of effective tobacco dependence treatments and reduce the leading cause of disease and premature death in the state – tobacco use.

Genetic research on smoking, in particular susceptibility to nicotine addiction, is currently underway with the hope that this will lead to innovative strategies for cessation and prevention of tobacco use. **Thomas Raffin, Ph.D.** of **Stanford University** has begun to examine some of the ethical and social issues that arise from this approach. He outlines the following preliminary scenario: it will take 10 years or more before genetic-based interventions are developed; many genes with weak effects will be identified instead of a single gene with strong effects; the genes will most likely play a role in addiction and in the inability to quit, rather than in the initiation of smoking.