



Annual Report
2000

Annual Report 2000

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

As we enter the 21st century, the United States and other developed countries have seen smoking rates fall for the past 35 years. The State of California has been a leader in this trend. In 1998, adult smoking prevalence was 18.4% compared to 24.1% for the whole U.S.^{1, 2} In fact, over the last decade cigarette consumption in California has declined at a rate of more than 1 ½ times that of the rest of the U.S and the lung cancer rate has declined by 14% as compared to 2.5% in the rest of the country. The singular event that propelled California into world-prominence in tobacco control was the voters' passage of Proposition 99, in 1988. Proposition 99 established state funding for comprehensive tobacco research and control activities by increasing the taxes on tobacco products. The California "model" has been praised around the world and held up as the standard to emulate.

California finds itself in a unique position to identify and understand new smoking and tobacco use norms from its burgeoning multi-racial and multi-ethnic population. Peoples from all over the Pacific Basin, especially Asian/Pacific Islanders and Latinos from Mexico, Central and South America are immigrating to California, bringing with them their own particular tobacco use histories, customs, and beliefs. This presents California researchers and tobacco control advocates with the challenge and responsibility to better understand the etiology of smoking-related cancers, lung disease, nicotine addiction, tobacco uptake prevention and tobacco use cessation among these populations. The findings derived from the research conducted among all of California's distinctive populations can serve as vital lessons for the rest of the United States and for many countries around the world.

In the past ten years, TRDRP has funded basic and applied research in biological and biomedical sciences, social and behavioral sciences, public health, epidemiology and public policy. It has supported 816 research grants at 68 California non-profit institutions with awards totaling over \$264 million. These include research into environmental tobacco smoke, sudden infant death syndrome (SIDS), ethnic and racial differences in smoking patterns, novel treatments for lung cancer, defining the detrimental cardiovascular impacts of smoking, the neurochemistry of nicotine addiction, and health effects of maternal smoking on fetal development. Additionally, it was engineering and epidemiological research funded by the program that helped lay the scientific foundation for the landmark legislation, AB 13, that outlawed smoking in indoor workplaces, including bars. Moreover, TRDRP has creatively developed funding strategies that strengthen the link between community-based and school-based tobacco control work with academic research. These Community Academic Research Awards and School Academic Research Awards, respectively, will improve the collaboration among the many and varied tobacco research and control activities in the State.

¹ Source: California Adults Tobacco Survey 1993-1999, Tobacco Control Section, California Department of Health Services, April 2000.

² CDC. Cigarette Smoking Among Adults – United States, 1998. MMWR 2000;49:881-4.

INTRODUCTION

As we enter the 21st century, tobacco researchers and tobacco control advocates, along with the Tobacco-Related Disease Research Program (TRDRP) are coming to grips with the sobering reality that tobacco use, especially cigarette smoking, continue as a growing global epidemic. With 1.1 billion smokers worldwide, and the tobacco industry successfully recruiting new smokers every day, tobacco-related disease will increase as the century progresses. The World Health Organization (WHO) estimates that 80 percent of tobacco-related deaths will take place in poorer nations, particularly countries in Africa, Asia, and Latin America. This situation desperately cries out for not only increased tobacco control efforts, but also amplified research programs to develop innovative, effective treatments for nicotine dependence and tobacco-related diseases, as well as new approaches to reduce tobacco use. In this regard, TRDRP is hopeful that U.S. state governments, including California, will take full advantage of the monies secured from the Master Settlement Agreement (MSA), to augment funds for tobacco research and control, rather than using these resources for mainly non-tobacco-related projects.

In contrast to the developing world, in the United States and other developed countries, smoking rates have fallen for the past 35 years. The State of California has been a leader in this trend. In 1998, adult smoking prevalence was 18.4% compared to 24.1% for the whole U.S.^{1,2} In fact, over the last decade cigarette consumption in California has declined at a rate of more than 1 ½ times that of the rest of the U.S. The singular event that propelled California into world-prominence in tobacco control was the voters' passage of Proposition 99, in 1988. Proposition 99 established state funding for comprehensive tobacco research and control activities by increasing the taxes on tobacco products. The California "model" has been praised at conferences around the world and held up as the standard to emulate. Despite this recognition, however, few other states and countries have implemented tax-supported comprehensive tobacco research programs. The MSA has provided the opportunity for other states such as Arizona, Colorado, Florida, Louisiana, Massachusetts, Minnesota, and Mississippi to develop state-sponsored research programs.

In the past ten years, TRDRP has funded basic and applied research in biological and biomedical sciences, social and behavioral sciences, public health, epidemiology and public policy. It has supported over ??? research grants at ?? California non-profit institutions with awards totaling over \$?????. These include research into environmental tobacco smoke, sudden infant death syndrome (SIDS), ethnic and racial differences in smoking patterns, novel treatments for lung cancer, defining the detrimental cardiovascular impacts of smoking, the neurochemistry of nicotine addiction, and health effects of maternal smoking on fetal development. Additionally, it was engineering and epidemiological research funded by the program that helped lay the scientific foundation for the landmark legislation, AB 13, that outlaws smoking in indoor workplaces, including bars. Moreover, TRDRP has creatively developed funding strategies that strengthen the link between community-based and school-based tobacco control work with academic research. These Community Academic Research Awards and School Academic Research Awards, respectively, will improve the collaboration among the many and varied tobacco research and control activities in the State.

California finds itself in a unique position to identify and understand new smoking and tobacco use norms from its burgeoning multi-racial and multi-ethnic population. Peoples from all over the Pacific Basin, especially Asian/Pacific Islanders and Latinos from Mexico, Central and South America are immigrating to California, bringing with them their own particular tobacco use histories, customs, and beliefs. This presents California researchers and tobacco control advocates with the challenge and responsibility to better understand the etiology of smoking-related cancers, lung disease, nicotine addiction, tobacco uptake prevention and tobacco use cessation among these populations. The findings derived from the research conducted among all of California's distinctive populations can serve as vital lessons for the rest of the United States and for many countries around the world.

TOBACCO-RELATED DISEASE RESEARCH PROGRAM (TRDRP) 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:

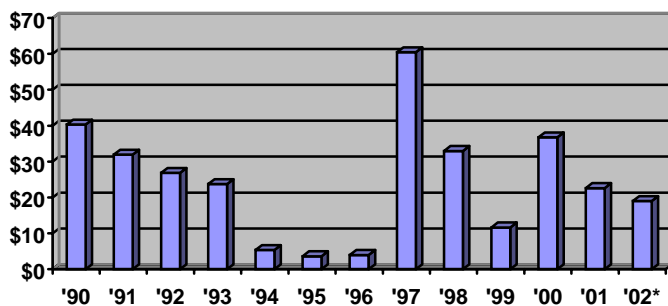
Providing opportunities to researchers to conduct high quality and innovative research that advances tobacco-related science.

Helping to build the research infrastructure critical for comprehensive tobacco-related disease research.

Funding History

From 1990-91 (first full year) to 1999-00, tobacco tax revenues have been declining and the research portion, set at 5% of annual tax revenues, also declined from \$26.9 million to \$20.2 million annually. Since most of the research funds are appropriated to the Tobacco-Related Disease Research Program, TRDRP should have shown relatively stable although 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 2. Appropriations of funds from 1990 to 2002. (*The value for 2002 is estimated.)
\$ are in millions



These fluctuations resulted from debates at the State level regarding the possible use of a portion of these resources for other programs. Ultimately, no funds were diverted; however, in some years, substantial portions of the annual revenues were held in reserve. As a result, TRDRP allocations after 1996 reflect not only annual revenues but allocations from accumulated reserves, creating the continued fluctuations in program funding seen from year to year, as pictured in Figure 2. An unfortunate consequence of the reduced funding in the mid 90's was a disruption of research projects, which substantially slowed the momentum gained in the earlier years. With the appropriation of the reserve funds, TRDRP has been able to restore investigator confidence in the program as a reliable funding source for research on tobacco use and tobacco-related disease.

Award Funding to Date

Since its inception, TRDRP has awarded investigators at 68 California institutions a total of 816 grants for more than \$264 million. The grants awarded constitute over 23 percent of the 3491 applications received. The number and dollar amounts funded by Subject Areas are as follows:

<i>Subject Area</i>	<i>Number</i>	<i>Dollars</i>
Cancer	164	\$44,741,975
Cardiovascular Disease	106	\$33,175,373
Epidemiology	101	\$42,593,225
General Biomedical	89	\$24,307,426
Tobacco Use Interventions	85	\$39,584,198
Nicotine Dependence	79	\$24,412,812
Public Health/Policy	84	\$23,681,119
Pulmonary Disease	108	\$32,093,064
Total	816	\$264,589,192

Current Portfolio

TRDRP's awards are made for up to three years and the currently portfolio numbers 322 active grants; these awards are listed in Appendix A.

Research Involving Women and Communities of Color

Of the 322 currently active grants, 162 (50%) involve humans subjects. Of the 162 human subject studies, 80 (49%) involve women subjects and 79 (49%) involve subjects from communities of color.

2000 FUNDING CYCLE

Research Priorities

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

Effects of Exposure to Secondhand Smoke

Epidemiological Research

Mechanism, Diagnosis, and Treatment of Tobacco-Related Disease

Nicotine Addiction and its Treatment

Policy/Economics Research

Prevention of Tobacco Use

Awards

In 2000, TRDRP awarded 92 grants for approximately \$33.3 million to investigators at 26 California institutions. These awards, which began July 1, 2000, constituted 36% of the applications reviewed. This percentage is slightly lower than the 42% in the previous year. Fewer grants will be awarded in 2001 because TRDRP's appropriation for 2000-2001 was only \$22.627 million, \$3.5 million less than expected.

2000 Award Distribution

<i>Subject Area</i>	<i># Awards (%)</i>	<i>Dollars (%)</i>
Health Effects	47 (51)	16,968,727 (51)
Nicotine Dependence	12 (13)	4,389,906 (13)
Interventions/Policy/ Behavioral Epidemiology	33 (36)	11,953,988 (36)
Total	92 (100)	33,312,621 (100)

<i>Funding by Award Type</i>	<i># Awards (%)</i>
Dissertation	9 (10%)
Postdoctoral Fellowship	5 (5%)
New Investigator	8 (9%)
IDEA	11 (12%)
CARA/SARA	5 (5%)
Research Project	54 (59%)

Details of all 2000 awards can be found in the TRDRP 2000 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/.

Dissertation Research Awards

Two years ago, TRDRP began to offer the Dissertation Research Award Mechanism. The response from the research community was somewhat disappointing. To stimulate interest in this award, TRDRP issued a special Call for Applications and increased its outreach efforts to raise awareness among researchers of its availability. This special attention proved successful and after peer review, and on the recommendation of TRDRP's Scientific Advisory Committee, the program made eleven dissertation awards that began 1/1/2000.

Cornelius Hopper Diversity Award Supplements

In honor of Cornelius L. Hopper, M.D., former UC Vice President for Health Affairs, the Cornelius Hopper Diversity Supplement Awards (CHDAS) were awarded for the first 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. Ten of our currently funded investigators have received supplements to their TRDRP grants for support of new personnel on their projects.

<i>Principal Investigator</i>	<i>CHDAS Trainee</i>	<i>Institution</i>
Larry Jamner	Emily Jamias	University of California, Irvine
Scott Carvajal	Roberta Downing	ETR Associates
Gregroy Talavera	Veronica Serrano	San Diego State University
Terry Conway	Yuriko Lopez	San Diego State University
Mark Alexander	Phelicia Jones	University of California, San Francisco
John Edmond	Diane Allen-Gipson	University of California, Los Angeles
Thomas Mack	Travis Alexander	University of Southern California
Jennifer Unger	Cara Booker	University of Southern California
Wendy Cozen	Nicole Stroud	University of Southern California
Francisco Villarreal	Laha Makhsudova	University of California, San Diego

2000 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. A complete bibliography for publications produced in the 1999-2000 fiscal year appears in Appendix C. Specifically, among the 159 citations, there 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*.

TRDRP sponsored a supplemental issue of *Tobacco Control*, the major international journal on this topic. The supplement features nine articles written by TRDRP-funded

investigators, highlighting the diverse research being conducted in California and its implications for the US and other countries.

On the occasion of its tenth anniversary, TRDRP published a summary of research funded by the program since its inception. TRDRP-funded research continues to yield new insight concerning the many problems resulting from tobacco use. *TRDRP: Research from 1990-2000* summarizes the many contributions made to the fields of tobacco control and tobacco-related disease by California investigators and show just how much knowledge has advanced over the last ten years. This TRDRP publications was posted on the program's website and approximately 1,600 copies were distributed to program stakeholders.

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.

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.

SARA/CARA 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. From the comments of the participants it was clear that this type of outreach was well received.

Conferences

In April, TRDRP participated in the planning of a TCS-sponsored conference entitled *Youth 2K and Beyond*.... The purpose of the conference was to share results of the Centers for Disease Control-funded Prevention Centers' youth and tobacco-related research with the California tobacco control professionals. By including tobacco prevention educators working in schools, the conference aimed at fostering improved communication and collaboration between local

school and community-based tobacco educators. The meeting concluded with consensus forums to determine, among other things, priorities for future research involving youth and young adults. Areas of high priority were research studies in ethnically and culturally diverse populations; research-based interventions for hard to reach youth and young adults; effective cessation treatments; marketing research; studies of the 'social smoking' phenomenon, especially initiation among 18-24 year olds, and its relationship to nicotine addiction; tobacco control policy research; studies of use of other tobacco products, including new tobacco products; and studies aimed at improving research methodologies. TRDRP has incorporated these areas into its research priorities for the coming years.

TRDRP participated in the 11th World Conference on Tobacco OR Health on August 6-11, 2000 in Chicago, Illinois. TRDRP co-sponsored a workshop for new tobacco investigators and also operated an exhibit booth during the conference. Many TRDRP-funded investigators presented their research at the meeting, which brought together more than 4,000 tobacco control professionals from all over the world.

TRDRP also co-sponsored a workshop on Environmental Tobacco Smoke at the International Society of Exposure Analysis Conference October 24-27, 2000 in Monterey, California. TRDRP funded the travel of several California TRDRP-funded investigators to present their findings at the workshop.

Other Activities

The TRDRP director continues to participate in a network of tobacco use research funders. The major supporters of tobacco research convene periodically to discuss a research agenda that includes all critical components for effective tobacco control; to develop cooperative and complementary research portfolios; and to coordinate requests for applications in areas of particular importance, such as youth tobacco cessation and smoking initiation among 18-24 year olds.

2001 FUNDING CYCLE

Budget for 2000-2001

Proposition 99 Research Account revenues in 2000-01 were estimated to be \$19.632 million. From this amount, \$5.1 million was earmarked for the Cancer Registry, which was \$3.55 million more than allocations in previous years. The appropriation for TRDRP for the 2000-01 fiscal year was thus \$14.48 million; however the appropriation was augmented by the final payment from the reserve, \$8.19 million, bringing the total appropriation to \$22.672 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 going to have a detrimental effect on the program's ability to achieve its goals.

Research Priorities

The Call for Applications and Application Packets for the 10th annual grant cycle in 2000-2001 was issued in September, 2000. The submission deadline for new applications is January 18, 2001, with funding for new awards slated to begin on July 1, 2001. 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, biochemistry, pathology – as well as translational 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 that relate 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 Secondhand Smoke

TRDRP is seeking to fund research that focuses on the biomedical impact of exposure to secondhand smoke. In addition to research on chronic ailments directly associated with tobacco smoke exposure (e.g., atherosclerosis), studies into the mechanisms, diagnosis or treatment of pulmonary diseases associated with childhood exposure to secondhand smoke (e.g., chronic bronchitis) or exacerbated by ETS (e.g., asthma) are encouraged. Important in this regard are quantifying and understanding the chronic effects of 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 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; 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

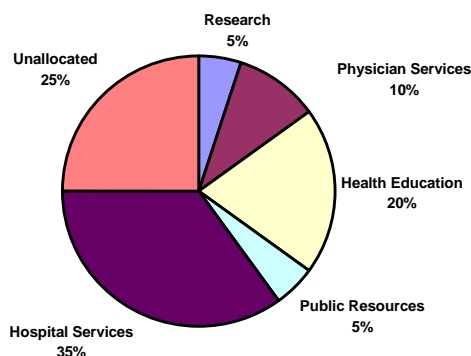
prevention and cessation, protection from secondhand smoke, and prevention, treatment, and diagnosis of tobacco-related diseases.

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: 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 1. 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. SAC members and the organizations they represent are listed in Appendix E.

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 research projects, which ended in 2000 are summarized below. The information presented here was taken from the final progress reports submitted by the principal investigators.

Disease Causes

Alan Fogelman, M.D. of the **University of California, Los Angeles**, looked at how cigarette smoke alters lipoprotein and artery wall interactions. He found that the concentration of the high density lipoprotein (HDL – “good” cholesterol) antioxidant enzyme paraoxonase was significantly lower in patients with normal lipids and coronary artery disease that smoked than in patients with normal lipids and coronary artery disease who did not smoke. Both groups of patients had lower levels of enzyme activity as compared to controls that had normal lipids, no cardiovascular disease, and did not smoke. The HDL from the smoking patients was significantly less protective against low density lipoprotein (LDL – “bad” cholesterol) oxidation by artery wall cells than was the HDL from non-smoking patients.

Jesse Joad, M.D. of the **University of California, Davis** has studied C-fibers, which are nerves that sense irritants in the lungs and cause rapid shallow breathing, narrowing of airways, mucous secretion, and breath holding when stimulated. Many of the same symptoms are reported in children who live in the homes with exposure to environmental tobacco smoke (ETS). Dr. Joad’s studies found that several aspects of the C-fiber reflex were enhanced by exposure to ETS. These data suggest that an increase in the responsiveness of C-fibers may explain some of the respiratory symptoms and sudden infant death that occurs in children raised with exposure to ETS. They also raise the possibility that drugs against a substance found in C-fibers, substance P, might be used in children raised with ETS to reduce their symptoms.

Thickening of the artery wall is a measure of early stage atherosclerosis. The thickness (IMT) and stiffness of the artery wall can be measured, using non-invasive ultrasounds of the carotid artery. Several epidemiological studies have demonstrated a positive relationship between greater carotid artery IMT and increased risk of cardiovascular events, including nonfatal and fatal heart attacks and strokes. Using measurements of IMT and arterial stiffness in a group of 993 subjects, **Wendy Mack, Ph.D.** of the **University of Southern California** found that both environmental tobacco smoke (ETS) exposure and active smoking are independent and important determinants of early stage atherosclerosis. The impact of ETS is apparent on subclinical atherosclerosis measured both by IMT and stiffness of the carotid artery.

Vitamin A and its natural and synthetic derivatives (retinoids) are effective agents in preventing the development of lung cancer. Unfortunately, clinical trials of retinoids in cigarette smokers have found lack of efficacy in preventing lung cancer, suggesting that cigarette smoking might impair retinoid activities. **Xiao-kun Zhang, Ph.D.** of **The Burnham Institute** studied whether nicotine inhibits the anti-cancer activities of vitamin A and the possibilities to suppress nicotine effects. Results show that nicotine induces cancer cell growth by abrogating the growth inhibitory effects of Vitamin A. The data also convincingly demonstrate the mechanism of nicotine action in cancer cells and possibilities of suppressing nicotine effects. The investigators

also found a class of anti-nicotine compounds that may be effective against tobacco-associated diseases.

Maternal cigarette smoking has a severe negative effect on all stages of pregnancy, from conception to birth. However, currently little is known about how maternal tobacco use is linked to a dramatic increase in infertility and serious pregnancy complications. **Susan J. Fischer, Ph.D.** and her colleagues at the **University of California, San Francisco**, hypothesize that smoking harms the placenta. The placenta is a transient organ that exists only during pregnancy. During this time the placenta carries out the roles of many of the fetus' important organs, including the heart, lungs, digestive system and kidneys. Thus, throughout this critical period toxic substances that harm the placenta likewise harm the developing child. Dr. Fischer's laboratory has found that the placenta is vulnerable to the toxic effects of maternal tobacco use. They have direct evidence that smoking interferes with the way placental cells grow and differentiate and they have also discovered that a protein causally linked to cancers in adults plays an important role in placental development during pregnancy.

Disease Progression

Daniel Steinberg, M.D., Ph.D. of the **University of California, San Diego**, developed a method to measure one of the earliest events in atherosclerosis, the infiltration of white blood cells (monocytes) into the artery. He and his research team have demonstrated the feasibility, sensitivity, and reproducibility of the method. They confirmed that certain molecules present on the surface of blood vessel cells stimulated monocyte recruitment. However, the rate of recruitment decreased as the extent of atherosclerosis increased. They also found that a new class of drugs used to treat diabetes affect monocytes and can protect against atherosclerosis in mice. The mechanism of the protection is not yet known and will require further investigation.

Huizhou Fan, Ph.D. of the **University of California, San Francisco** studied how a growth factor called TGF-alpha contributes to the development of lung cancer. Results of the study showed that in normal tissues, TGF-alpha is largely retained by the producer cells and therefore only stimulates the producer cells themselves or cells in their immediate vicinity. However, in cancer cells, TGF-alpha is released into tissue fluid surrounding the cells. The freely diffusible TGF-alpha can then stimulate the growth of cells at appreciable distance from the producer cells. This work is not only leading us to a better understanding of cancer progression, but is also contributing to the development of new therapeutic strategies for cancer treatment, since inhibition of the ability to release TGF-alpha can stop the growth and spread of cancer cells.

Early Detection

Sotirios Tsimikas, M.D. of the **University of California, San Diego**, developed a noninvasive method to image atherosclerotic lesions. Specific antibodies intravenously injected into animals accumulate specifically within atherosclerotic lesions but not in normal tissue. The signal generated by the antibody within the atherosclerotic plaque is proportional to the amount of oxidized low density lipoprotein (LDL) and atherosclerotic lesions present. Because of potentially serious side effects of the mouse antibodies in humans, Dr. Tsimikas has begun to

develop human antibodies that would have fewer side effects. Potential applications of these techniques may include noninvasive diagnosis of narrowed arteries due to atherosclerosis, selection of optimal candidates for drug/dietary intervention based on results of imaging, and to follow the natural progression or regression of these lesions.

Chewing or smoking tobacco is the main cause of oral cancer, a condition which claims the lives of almost 10,000 people in the U.S. each year. Because of the difficulty in detecting oral cancer early, it has one of the worst survival rates of all major cancers. **Petra Wilder-Smith, D.D.S., Ph.D.** of the **University of California, Irvine**, investigated the use of fluorescence for non-invasive early diagnosis of potential precancers and cancers in hamster cheek pouches, which best simulate conditions in the human mouth. The data showed that non-invasive fluorescence measurements can be used for the early detection of premalignant or malignant changes in the mouth. This information brings us one step closer to developing a sensitive and accurate tool for the early detection, diagnosis, and monitoring of oral lesions. This will prevent much pain and suffering and reduce treatment costs.

Pancreatic cancer is one of the most lethal of human diseases. It is the fourth leading cause of cancer-related deaths among men and women in the United States. The average 5-year survival is less than 5%. Numerous scientific studies designed to reveal the causes of pancreatic cancer have consistently identified cigarette smoking as a significant risk factor. In fact, cigarette smoking remains the only well-established risk factor for pancreatic cancer. The diagnosis of pancreatic cancer currently requires sophisticated medical technology. A simple blood test that is able to indicate whether pancreatic cancer is present would represent a major step toward the early diagnosis of pancreatic cancer. Early diagnosis followed by surgery is currently the only hope for patient survival. **Anson Lowe, M.D.** of **Stanford University** has developed a blood test for a protein, GP2, which is made only in the pancreas and is released into the bloodstream with pancreatic disease. He and his colleagues were able to generate human antibodies to the protein and were successful in developing a sensitive test for GP2. Initial results show that GP2 levels are significantly elevated in patients with pancreatic cancer and other pancreatic diseases. However, the sensitivity is still less than desired for a useful screening tool. The usefulness of the assay in pancreatic cancer will be determined as more patients are enrolled in the study.

Treatment

Matthew Brenner, M.D. of the **University of California, Irvine**, conducted a study to optimize the effectiveness of lung volume reduction surgery (LVRS) for emphysema using animal models. The objectives were to investigate physiologic mechanisms of response to LVRS in order to 1) improve operative response to LVRS, 2) refine selection criteria, and 3) evaluate specific working animal models for future studies. The investigators were able to improve their animal model to generate moderately severe emphysema and are now working on trying to generate even more severe degrees of emphysema. The investigators have also looked at variables that govern optimal resection. They found that resting baseline or intraoperative variables may not be accurate predictors of optimal outcome. This project may help advance the knowledge and treatment of lung disease specifically directed towards LVRS approaches to emphysema, as well as the more general understanding of physiologic responses of patients with emphysema.

Francis Szoka, Ph.D. of the **University of California, San Francisco**, developed a new targeted chemotherapy to treat lung cancer. The purpose was to reduce the toxicity of the drug to the normal tissue by directing the drug to the tumor cells with a drug delivery system. This is similar in concept to the use of a cruise missile to only destroy a military target. Targeting drug delivery to lung tumors may prove to be the most efficacious and economical means by which to treat lung cancer since groups of tumor cells that have spread away from the main tumor and are too few in number to be detected can be exposed to a high level of drug by these ‘smart bombs’. The smart bomb in this research is a liposome, which is a microscopic balloon formed from lipids. Cytotoxic drugs can be carried inside the liposome where they do not come into contact with the cells. The lipids can be broken down by metabolism inside the body and the drug is then released. Liposomes are now used in human patients to treat solid tumors but they are not yet effective for treating lung tumors because the currently available liposomes do not stick to the lung tumors. Dr. Szoka’s laboratory has found a promising polymer that may make it possible to target liposomes to lung tumors, which they will study further to optimize its properties for treatment.

Michael Kelner, M.D. of the **University of California, San Diego** continues his work on Illudins, natural products with novel chemical structure isolated from the toxic Jack O’Lantern mushroom, which grows throughout California. Dr. Kelner’s laboratory has been developing novel chemotherapeutic agents from these Illudin toxins for treatment of non-small cell lung cancer (NSCLC), which is the main type of lung cancer caused by smoking. The current therapy for NSCLC has limited effect, in part because many patients with NSCLC have tumors that have spread to other sites of the body (metastases). These patients often relapse after initial treatment. The TRDRP-sponsored studies have identified a new class of anticancer agents active against cancer resistant to conventional therapy. One of these agents (Irofulven) is now in final or phase III human trials in an effort to obtain FDA approval.

Nicotine Addiction

Nicotine dependence arises from the interaction of nicotine with a macromolecule in the brain termed the nicotinic acetylcholine receptor (nAChR). Binding of nicotine or the neurotransmitter, acetylcholine, activates the receptor. This causes the receptor to open to allow charged particles like calcium and sodium ions to pass through, thus acting as a channel for the propagation of electrical information from the brain to various tissues. In order to understand how nicotine interacts with its target, **Siobhan Malany, Ph.D.** of the **University of California, San Diego**, sought to identify key components of the nAChR involved in binding nicotine and to delineate the relative spatial arrangement of these components at the binding interfaces. The results of this study have revealed new information of where nicotine binds and how it interacts with the receptor.

The mechanism of nicotine dependence is not known and it is necessary to understand how nicotine exerts its effects on the nervous system. **Stephen Heinemann, Ph.D.** of **The Salk Institute for Biological Studies**, is conducting research aimed at contributing to the molecular and neurobiological understanding of nicotine dependence and addiction to enable the development of rational strategies to help people stop smoking. The goal of the research was to

look for novel proteins, which regulate nicotinic receptor function. The investigators identified two promising genes that they plan to test for activity in the nicotinic receptor regulatory mechanisms. Identification of nicotinic receptor regulatory proteins may make it possible to develop drugs that reverse the changes that take place in the brains of smokers, which may help them stop smoking.

In another approach to the understanding of nicotine tolerance and dependence, **Henry Lester, Ph.D.** of the **California Institute of Technology** is genetically altering parts of the nicotinic receptors to gain insights about how nicotine alters receptor function.

Darwin Berg, Ph.D. of the **University of California, San Diego** has identified a new kind of nicotinic receptor in rats, which contains the $\alpha 7$ subunit. This type of receptor is widely expressed in the nervous system and regulates numerous calcium-dependent cellular events due to its high relative calcium permeability. Due to this characteristic, the receptor has been implicated in numerous brain functions and neurodegenerative diseases.

Tobacco Control Interventions

Since nicotine patches and gum became available in 1996, their sales have increased 152%. Because the products are designed for use by the general public, patients are now able to self-prescribe and self-treat their addiction without the proven positive effects of professional intervention. Although the availability of pharmaceutical aids for tobacco cessation renders the pharmacist as a logical candidate for providing intervention to tobacco users, a survey of pharmacists conducted by **Karen Hudmon, Dr.P.H., R.Ph.** of **SRI International**, showed that less than 8% of respondents have had formal training for providing tobacco cessation counseling. Ninety-three percent indicated that receiving specialized training would increase the quality of their counseling, and 70% indicated that it would increase the number of patients that they counsel. Based on these results, Dr. Hudmon and her team have developed 6-hour tobacco curriculum that, as of the year 2000, will be required coursework for all pharmacy students in California. By serving as an interface with the health care system for tobacco users, pharmacists are uniquely positioned to be a cornerstone for tobacco cessation efforts.

Smoking among children and adolescents has tremendous public health importance. Onset and development of smoking occurs primarily in adolescence, and because tobacco is highly addictive, regular use develops into nicotine dependency. Smoking in adolescence is likely to continue into the adult years, increasing the risk of numerous long-term negative health consequences. Despite three decades of efforts to prevent youth smoking, large numbers of young people continue to smoke, particularly teens who engage in other high-risk behaviors. Unfortunately, adolescent smokers are difficult to recruit and retain in smoking cessation interventions. Even more discouraging, cessation interventions that have been effective with adults have not shown much promise with youth. **Susan Woodruff, Ph.D.** of the **San Diego State University**, pilot-tested an innovative approach to adolescent smoking cessation using an internet-based 3-dimensional “world” in which young smokers interact (i.e., chat) in real-time with a trained cessation facilitator and each other. This approach capitalizes on the demonstrated benefits of facilitator-led, structured, motivational interviewing strategies, as well as peer-to-peer interaction. High-risk teen smokers volunteered for this study, participated at high levels, and

rated the approach very positively. Participants showed statistically significant changes in reports of quitting, amount smoked, and intentions to quit. The chat room approach showed high feasibility and acceptability, and may be effective in a population that is resistant to quitting smoking.

It is widely recognized that improving health promotion of special populations requires community-based interventions in the target community. **Ana Navarro, Ph.D.** of the **University of California, San Diego** and **Beatriz Roppé** of the **Sherman Heights Community Center** completed a pilot project, *Por La Vida*, which capitalized on the use of existing social networks in the Latino community. Previous Por La Vida projects have successfully reached out to the Latino population of low socioeconomic level and low level of acculturation through health education programs. This pilot project enhanced the empowerment of the Latino community to build smoke-free environments themselves. The project successfully examined the feasibility of a community-intervention in the predominantly low income Latino community in Southeast San Diego. In addition, members of the community at the center of the intervention also participated in the pilot testing of evaluation instruments. This pilot project resulted in a three-year implementation study, which is currently ongoing.

Clyde Dent, Ph.D. of the **University of Southern California** evaluated the effectiveness of a cessation program using nicotine replacement products, such as nicotine patches and gum, for smokeless tobacco users trying to quit. Participants in the program who used nicotine patches in addition to the behavioral program had higher quit rates than those who did not use nicotine patches: 36% vs. 18% at three months, and 45% vs. 13% at six months. Adding nicotine gum in addition to the nicotine patches, enhanced quit rates at three months (58% vs. 36%) but this effect was lost at 6 months (45% for both groups). This study shows that use of nicotine replacement therapy is an effective strategy for smokeless tobacco cessation.

In 1998, 60% of high school students surveyed in Lake County had tried smoking and 36% were self-reported regular smokers. To address this problem, a collaborative partnership, led by **Lilian Hoika** and **Margaret Walsh, Ed.D.**, between staff at **Lake County Office of Education**, **Sutter Lakeside Community Services**, the **Lake County Health Services Department**, and researchers at the **University of California, San Francisco**, was formed to conduct a pilot study with the aims to 1) identify psychosocial factors and intervention components related to successful tobacco cessation for adolescent smokers; 2) collaborate with faculty and students from Carle High School computer technology educational program to develop a computer program to “morph” digital photographs of students to simulate physical appearance changes related to tobacco use and/or oral cancer; and 3) pilot test a tobacco cessation intervention for feasibility and acceptability among high school-age adolescents attending one high school in rural Lake County. Findings from this pilot study indicate that the program is feasible and acceptable; that nicotine addiction in adolescents needs to be addressed; that adolescent tobacco users might be motivated to quit based on tobacco-related adverse effects on physical attractiveness; that all students should be offered the opportunity to participate in the oral and skin care screenings and computer simulations; and that counseling sessions should be gender specific.

Social/Behavioral Research

Xinguang Chen, Ph.D. of the **University of Southern California** described patterns of cigarette use among Asian Americans in California in order to identify factors associated with their cigarette smoking behavior, and to test the role of acculturation in their cigarette use in general and by subgroups of Chinese, Filipino, Japanese, and Korean Americans. Asian Americans smoke less than other ethnic minority groups but variation in smoking prevalence within Asian subgroups was greater than between Asian and other ethnic groups. The age of smoking initiation was older for Asian Americans than for others. While many of the factors associated with cigarette smoking in other ethnic groups were also associated with cigarette smoking by Asian Americans, Asian American adolescents tend to be influenced more by smoking parents, and less by smoking siblings/friends and pro-tobacco media.

Policy Research

Karen Butter of the **University of California, San Francisco**, directs the Tobacco control Archives (TCA) which were established in 1994 with TRDRP funding to document tobacco control policies and the anti-smoking movement in California and to provide a central and organized repository for unpublished information. TCA continues to receive records from parties involved in tobacco control in California. Almost 90% of the archival collections TCA has received in the last 6 years have been processed and are available for research use. TCA serves as a gateway for researchers to TCA's specific holdings and to the world of tobacco control information at large. TCA's holdings were used in one documentary television project from Paris, France public broadcasting.

In an innovative community-intervention project aimed at reducing sales of cigarettes to youth, parents and adults from the community were trained to conduct the intervention. The goal of the intervention was to motivate adults in the community to object when they observed sales of tobacco to youth, and to shop only in stores that did not do so. **Hope Landrine, Ph.D.**, of the **Public Health Foundation Enterprises, Inc.** found that tobacco sales to youth decreased after the intervention, but only a portion of the decrease could be attributed to the intervention. Therefore, the findings from the study tentatively suggest that changing community attitudes and behaviors might be added to current merchant-education efforts to maximize the success of efforts to reduce youth access to tobacco.