



# Annual Report 2003

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

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## EXECUTIVE SUMMARY

Tobacco consumption in California is at an all-time low due to an effective, comprehensive state tobacco control program and increases in state excise taxes on tobacco and the price of tobacco products. Unfortunately, the need for continued research on tobacco-related disease and tobacco use has not declined with the drop in the number of cigarettes smoked. For decades to come, the state's taxpayers will be paying for the treatment of tobacco-related diseases that are now developing in California's current smokers and in adolescents who are starting to smoke. According to a report by the Institute for Health & Aging at the University of California, San Francisco, the cost of smoking in California is nearly \$16 billion annually, or \$3,331 per smoker every year, an avoidable cost borne by all California taxpayers.<sup>1</sup>

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

The decline in smoking has resulted in reduced revenue for the state's programs for tobacco-related disease research and tobacco control because they are funded by a portion of the revenue collected from the tobacco excise surtax imposed when California voters passed Proposition 99 in 1988. In 2003, TRDRP was unable, because of limited funds, to fund 41 research grant applications that had been rated "excellent" by expert peer reviewers. In light of TRDRP's inability to meet all research needs on tobacco-related disease, the program used strategic planning to determine achievable goals over the next several years. This process, which included consultation with researchers, tobacco control experts, and voluntary health organizations, resulted in the identification of primary research topics that are receiving high priority for funding in the 2004 grant cycle.

In the 2003 funding cycle, TRDRP awarded 57 grants for a total of \$19,476,242 to investigators at 25 California institutions to address the following research priorities:

- Tobacco control among under-studied populations in California
- Differences among men and women in smoking-related disease and in prevention and cessation of tobacco use
- The health needs of current or former smokers
- The new generation of tobacco products
- Prevention of tobacco use
- Tobacco constituents that contribute to tobacco-related disease and addiction
- Secondhand smoke exposure

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<sup>1</sup> Max, W. et al. The Cost of Smoking in California, December 2002.

# INTRODUCTION

Tobacco consumption in California is at an all-time low due to an effective, comprehensive state tobacco control program and increases in state excise taxes on tobacco and the price of tobacco products. Unfortunately, the need for continued research on tobacco-related disease and tobacco use has not declined with the drop in the number of cigarettes smoked. For decades to come, the state's taxpayers will be paying for the treatment of tobacco-related diseases that are now developing in California's current smokers and in adolescents who are starting to smoke. According to a report by the Institute for Health & Aging at the University of California, San Francisco, the cost of smoking in California is nearly \$16 billion annually, or \$3,331 per smoker every year, an avoidable cost borne by all California taxpayers.<sup>2</sup>

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## TOBACCO-RELATED DISEASE RESEARCH PROGRAM TO DATE

### Mission and Goals

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

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

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

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<sup>2</sup> Max, W. et al. The Cost of Smoking in California, December 2002.

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

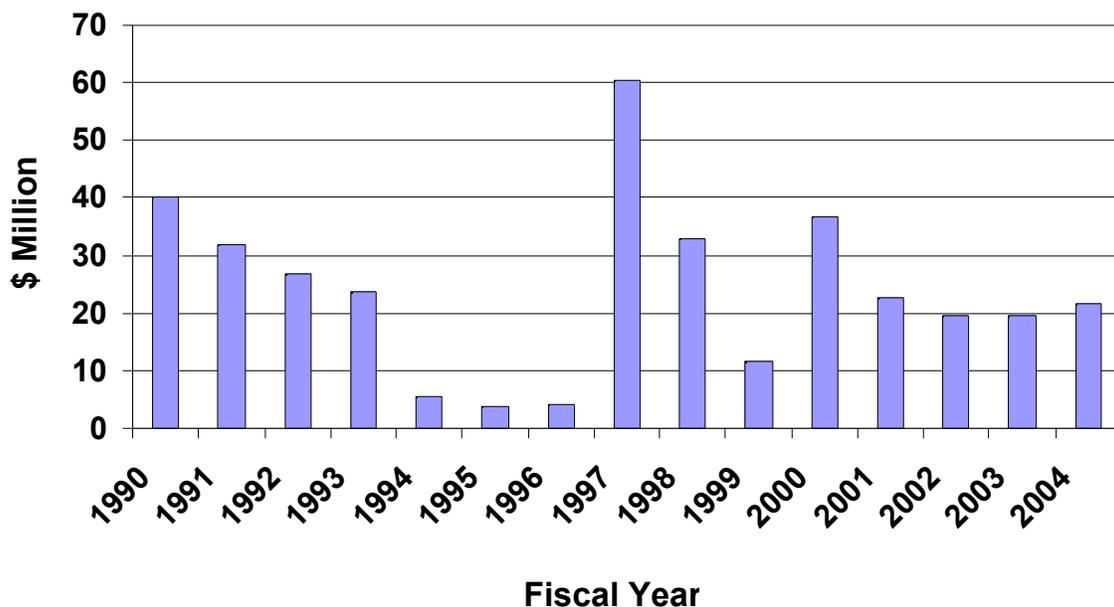
TRDRP strives to meet the needs of the research community by:

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

### Funding History

The sole source of TRDRP funds is the revenue from the tobacco surtax that was established when California voters passed Proposition 99 in 1988. Proposition 99 specified that five percent of this tax revenue be deposited in the Research Account and that it be used for research on tobacco-related disease. Tobacco sales in California have steadily declined since the Proposition 99 tobacco excise surtax went into effect in 1989. Between 1990-91 and 2002-04, TRDRP resources declined from \$26.9 million to \$21.6 million annually. Appropriations from the Research Account to the University of California have shown large fluctuations – from \$40.3 million in 1990 to \$3.65 million in 1995 to \$60.4 million in 1997 (see Figure 1).

**Figure 1: Appropriations to TRDRP from Proposition 99 Research Account, 1990-2004**



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

in 1999-2000 it was 7.5 percent. Starting in 2000-2001, however, the DHS appropriation was increased to approximately \$5 million which is now 24 percent of the total available.

### **Award Funding to Date**

Since its inception in 1989 through 2003, TRDRP has awarded \$327 million in 1,019 grants to scientists at 76 California institutions. The grants awarded constituted 24 percent of the 4,233 applications received. The number and dollar amounts funded by subject area are displayed in Table 1.

**Table 1: Award Totals by Subject Area**

<i>Subject Area</i>	<i>Amount</i>	<i>Number</i>
Cancer	\$56,348,116	204
Cardiovascular Disease	\$41,485,804	128
Epidemiology	\$50,731,782	127
General Biomedical Science	\$28,526,173	104
Tobacco Use Interventions	\$50,082,578	115
Nicotine Dependence	\$33,706,703	110
Public Health/Policy	\$29,038,765	104
Pulmonary Disease	\$36,960,513	127
<b>Total</b>	<b>\$326,880,434</b>	<b>1,019</b>

### **Research Involving Women and Communities of Color**

Of TRDRP’s 257 active grants, 131 (51 percent) involve human subjects. Of these, 43 (33 percent) involve women subjects and 44 (34 percent) involve subjects from communities of color. An additional six grants are conducting secondary analyses of data originally collected from human subjects. All six of these involve both women subjects and subjects from communities of color.

## **2003 FUNDING CYCLE**

### **Research Priorities**

The research priority areas in the 2003 funding cycle were the following:

- Tobacco control among under-studied populations<sup>3</sup> in California
- Gender-based differences in smoking-related disease and in prevention and cessation of tobacco use
- The health needs of current or former smokers
- The new generation of tobacco products
- Prevention of tobacco use
- Tobacco constituents that contribute to tobacco-related disease and addiction
- Public policies and programs for tobacco control
- Secondhand smoke exposure

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<sup>3</sup> “Under-studied populations” are groups of Californians who are believed to have higher rates of tobacco use and to suffer disproportionately from tobacco-related disease. Examples are low-income residents and ethnic and racial groups. Further research is required to provide better evidence regarding the incidence, prevalence, morbidity, mortality, and nature of tobacco-related disease in these communities.

## 2003 Awards

In 2003, TRDRP awarded 57 grants for a total of \$19,476,242 to investigators at 25 California institutions. These awards constituted 24 percent of the applications reviewed.

**Table 2: 2003 Awards by Subject Areas**

<i>Subject area</i>	<i>Number of awards</i>	<i>Percent</i>	<i>Amount awarded</i>	<i>Percent</i>
Cancer	11	19%	\$4,134,573	21%
Heart and lung disease	8	14%	\$2,698,461	14%
Epidemiology and other health effects	12	21%	\$3,565,599	18%
Nicotine dependence	8	14%	\$2,865,212	15%
Tobacco use prevention and cessation	10	18%	\$3,596,904	18%
Public health and policy	8	14%	\$2,609,893	13%
<b>Total</b>	<b>57</b>	<b>100%</b>	<b>\$19,470,642</b>	<b>100%</b>

**Table 3: 2003 Awards by Type**

<i>Award type</i>	<i>Number of awards</i>	<i>Percent of applications funded</i>
Research Project	24	19.2%
IDEA	4	11.4%
Community-Academic	2	15.4%
School-Academic	1	33.3%
New Investigator	9	32.1%
Postdoctoral Fellowship	11	39.3%
Dissertation	6	50.0%
<b>Total</b>	<b>57</b>	<b>23.4%</b>

Details of 2003 awards, including abstracts, can be found in TRDRP's Compendium of Awards, which can be accessed on the web at [www.trdrp.org](http://www.trdrp.org), or obtained from the program office ([trdrp@ucop.edu](mailto:trdrp@ucop.edu) or 510-987-9870).

## Cornelius Hopper Diversity Award Supplements

The Cornelius Hopper Diversity Award Supplements (CHDAS) are designed to encourage TRDRP-funded principal investigators to mentor individuals who want to pursue careers in research on tobacco use and tobacco-related disease. Qualified applicants for the CHDAS are from groups that are underrepresented among researchers who investigate tobacco use or tobacco-related disease, and/or individuals who will work directly with underrepresented groups that are disproportionately impacted by tobacco use. Three currently funded investigators received supplements to their TRDRP grants for support of new project personnel (see Table 4).

**Table 4: CHDAS awarded in 2003**

<i>CHDAS Trainee</i>	<i>Education</i>	<i>Principal Investigator</i>	<i>Institution</i>
Naira Serobyán	Post-doctoral	Sophia Khaldoyanidi	La Jolla Institute for Molecular Medicine
Luis Quinones	Post-baccalaureate	Ricardo Muñoz	University of California, San Francisco
Joann Lee	Graduate	Susan Woodruff	San Diego State University

## **DISSEMINATION OF RESEARCH FINDINGS**

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

### **Scientific Publications**

TRDRP-funded investigators have continued to actively disseminate findings from their research in scholarly publications and at scientific conferences. In 2003, funded investigators reported publishing 220 articles in refereed scientific journals, including 156 that had appeared in print and 64 that were accepted for publication and were awaiting appearance in print. These are increases in productivity over 2002. Some of the peer-reviewed scientific journals in which the papers appeared include: *Addictive Behaviors*; *American Journal of Epidemiology*; *American Journal of Public Health*; *Brain Research*; *Cancer Epidemiology, Biomarkers, and Prevention*; *Cancer Research*; *Cardiovascular Research*; *Cell*; *Circulation*; *Health Economics*; *Journal of Biological Chemistry*; *Journal of Consulting and Clinical Psychology*; *Journal of Neuroscience*; *Nicotine and Tobacco Research*; *Preventive Medicine*; and *Tobacco Control*.

### **Annual Investigator Meeting 2003**

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

More than 300 researchers and tobacco control practitioners attended TRDRP's seventh Annual Investigator Meeting (AIM 2003) in San Diego on December 3-4, 2003. The conference theme was "Investigate, Translate, Disseminate: Research for a Healthier Tomorrow." AIM 2003 began with a keynote address on the legislative perspective on tobacco control in California by State Senator Deborah Ortiz, Chair of the Senate Health and Human Services Committee. Due to a conflict her speech was delivered by her Chief Consultant Roger Dunstan.

TRDRP co-sponsored the following five workshops:

- “Nicotine Dependence Treatment – New Perspectives” organized by the Scripps Research Institute.
- “Advances in Secondhand Smoke Exposure Assessment” organized by Lawrence Berkeley National Laboratory.
- “Bringing New Evidence to Benefit Patients: From the Lab to Treatment, Screening, and Prevention” organized by the American Cancer Society, California Division.
- “Research Approaches to Smokefree Workplace Policy” organized by the Pacific Institute for Research and Evaluation.
- “Environmental Tobacco Smoke and Adverse Pregnancy Outcomes” co-sponsored by the California Department of Health Services’ Tobacco Control Section and TRDRP.

The second day began with a plenary session on the conference theme of research translation, moderated by Jeannette Noltenius, Ph.D., Vice President of Swartz & Associates. It included informative and stimulating talks by Ronald Goldfarb, Ph.D., President & CEO of Sopherion Therapeutics, Inc.; the Reverend Ted Greer, Jr., Director of Healthy Body, Healthy Soul; and Glen Morgan, Ph.D., Program Director of the Tobacco Control Branch of the National Cancer Institute.

The conference concluded with a Town Hall Meeting on “Nicotine Replacement Therapy,” currently a controversial topic in tobacco use cessation. The primary question concerns the effectiveness of nicotine replacement products (e.g., the patch) when sold over-the-counter.

Attendees had opportunities on both days to view and discuss the research findings summarized in poster presentations by TRDRP-funded investigators.

## **Newsletter**

In 2003, TRDRP published three issues of its newsletter, *Burning Issues*, which contained articles on critical research topics in tobacco-related disease and tobacco use, and information about the program and notices of upcoming events. The newsletters are posted on TRDRP’s website ([www.trdrp.org](http://www.trdrp.org)) and approximately 3,000 hard copies were mailed to program stakeholders.

In addition to program news and updates, the 2003 newsletters included articles on research funding for lung cancer; the efficacy of over-the-counter sales of nicotine replacement therapy (the “patch”); the Privacy Rule of the Health Insurance Portability and Accountability Act of 1996 (HIPAA), which is the federal government’s standards to protect patients’ medical records; the tobacco industry’s influence in the state legislature; and the reduction and elimination of tobacco research and control programs in other states.

## **Website**

Visitors to TRDRP’s website ([www.trdrp.org](http://www.trdrp.org)) can search research grants, as well as view all program publications and announcements.

## **Conferences**

Program staff gave presentations or organized and moderated workshops by TRDRP-funded investigators on: (1) smoking by African Americans at the Mayo Clinic’s annual nicotine dependence conference; (2) community and school research partnerships at the annual meeting of the Community-Campus Partnerships for Health; and (3) new directions in tobacco control

research at the annual project directors meeting of the California Department of Health Services' Tobacco Control Section.

During 2003, TRDRP staff participated in the following national and state conferences to learn the latest scientific developments and to network with scientists who are potential applicants or peer reviewers: youth and tobacco, the tobacco industry documents, and state and federal government research, sponsored by the National Cancer Institute; tobacco control research, sponsored by the National Cancer Institute; LGBT National Action Plan on Tobacco; the National Conference on Tobacco or Health; annual meeting of the American Society for Cell Biology; National Chronic Obstructive Pulmonary Disease conference; National Summit on the Primary Prevention and Early Detection of Cancer sponsored by the National Dialogue on Cancer; American Lung Association of California Annual Meeting; Latino Council on Alcohol and Tobacco; Sex Differences in Lung Cancer Conference sponsored by the Society for Women's Health Research.

## **TRDRP COLLABORATIONS**

TRDRP actively participated in tobacco control activities in California, other states, and nationally. TRDRP co-sponsored a workshop on tobacco industry funding and scientific research February 22-23, 2003 in New Orleans. Other sponsors were the American Legacy Foundation, the National Cancer Institute, and the Society for Research on Nicotine and Tobacco. TRDRP organized and moderated a session at the Tobacco Control Section's 2003 Project Directors Meeting, April 7-10 in Newport Beach. The speakers addressed new directions for tobacco control research with California's Hmong, African American, and Latino communities. They discussed the use of tobacco industry documents, smoking and reproductive health, and the use of the internet for smoking cessation. A senior staff member organized a workshop titled "How to Create and Maintain Community-School Academic Research Partnership for Change" at the annual meeting of Community-Campus Partnerships for Health, a national non-profit organization, April 26-29, 2003 in San Diego. TRDRP-funded investigators presented the results of their research. TRDRP co-sponsored with other leaders in the state's tobacco control community the "Priority Populations Conference: Weaving Our Message – United Against Tobacco Abuse," October 14-15, 2003 in Los Angeles.

A senior TRDRP staff member served on the Board of Directors of the California Tobacco Control Alliance, which is funded primarily by a Smokeless States Grant from the Robert Wood Johnson Foundation. The Alliance's goal is to reduce tobacco use through statewide implementation of an evidence-based model smoking cessation program throughout California's managed care delivery system.

TRDRP collaborated with other organizations to share California's experiences and to learn from research efforts in other states and nationwide. TRDRP continued to conduct the peer review of research grant applications for the Colorado Tobacco Research Program and a senior staff member participated in the review of grant proposals for the Minnesota Partnership for Action Against Tobacco.

## 2004 FUNDING CYCLE

### Budget for 2003-04

The 2003-04 Budget Act appropriated \$23,863,000 to the University of California for TRDRP. This was an increase of \$4,429,000 (23%) over the 2002-03 appropriation of \$19,434,000, comprised of \$2,000,000 from the Proposition 10 tobacco tax revenues and \$2,429,000 from the reserve in the Proposition 99 Research Account. The Governor's proposed 2004-05 budget reduced the 2003-04 appropriation by \$2,238,000 (9%) to \$21,625,000 and reduced the 2004-05 appropriation by an additional \$7,372,000 (34%) to \$14,253,000. These reductions were due primarily to a projected decrease in Proposition 99 revenue and the depletion of the reserve in the Research Account.

For the fourth consecutive year, the Department of Health Services received an increased appropriation from the Proposition 99 Research Account for the California Cancer Registry and the Environmental Health Investigations Branch. However, the redirection of already diminishing funds is having a detrimental effect on the program's ability to achieve its goals. In light of TRDRP's inability to meet all research needs on tobacco-related disease, the program implemented recommendations from a strategic planning process completed last year.

### Research Priorities

The Call for Applications and Application Packets for the 13<sup>th</sup> annual grant cycle were issued in fall 2003. The application submission deadline was January 15, 2004, with funding for new awards slated to begin July 1, 2004.

TRDRP solicited applications for research into: the etiology, pathogenesis, earlier detection, diagnosis, and treatment of tobacco-related disease; novel methods for tobacco use prevention and cessation; and the development, implementation, evaluation, and dissemination of tobacco control policies. In a major change for the 13<sup>th</sup> grant cycle, proposals addressing the following primary topics for Research Project Awards will be given an advantage in the funding decisions:

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

### Award Types

- **Research Project Awards** fund investigator-initiated research projects on all aspects of tobacco-related disease and tobacco use. These awards support research that is judged likely to yield valuable outcomes. The projects are judged to be feasible and likely to succeed because they employ sound scientific approaches and offer promising supporting data from preliminary studies.
- **Innovative Developmental and Exploratory Awards (IDEAs)** fund developmental or exploratory research that is not yet sufficiently mature to compete successfully for an individual research award. Although the proposed research might lack adequate pilot data or proven methods, it is creative, intellectually exciting, and shows clear promise to yield findings that could lead to breakthroughs in the field.

- **Research career development awards.** TRDRP offers three award types that are aimed at enhancing the scientific infrastructure for tobacco-related research in California by supporting the development of careers in research. **New Investigator Awards** are aimed at encouraging newly independent investigators to conduct research on tobacco-related issues. **Postdoctoral Fellowship Awards** allow researchers early in their careers to receive training in tobacco-relevant disciplines. **Dissertation Research Awards** provide support for the dissertation research of doctoral candidates who wish to pursue tobacco-related research.
- **Collaborative research awards. Community-Academic Research Awards (CARA)** are intended to stimulate and support collaborations between community-based organizations and university-based investigators to perform scientifically rigorous research into tobacco control issues important to California’s diverse communities. **School-Academic Research Awards (SARA)** are intended to stimulate and support collaborations between schools and university-based investigators to perform scientifically rigorous research into tobacco control issues that: 1) are identified as important to schools in the state; 2) are likely to produce results that are meaningful to school-based prevention and intervention efforts; and 3) use methods that are relevant, culturally appropriate, and appropriate in terms defined and accepted by the schools. SARAs are jointly funded by the California Department of Education (CDE) and TRDRP.

## **Evaluation of Research Grant Applications**

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

## **TRDRP HISTORY**

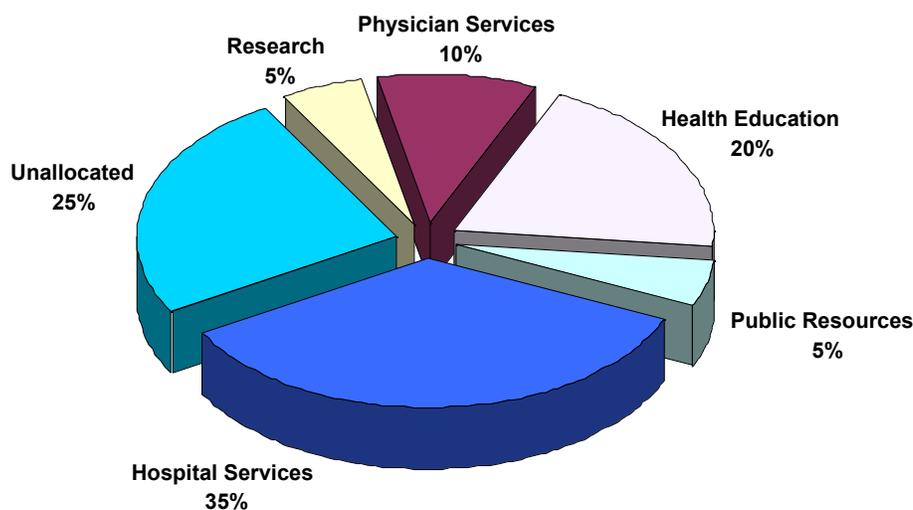
### **Program Administration**

TRDRP was established as a result of the passage of Proposition 99 (“The Tobacco Tax and Health Protection Act of 1988”) in November 1988. The proposition increased the tax on cigarettes by 25 cents per pack and raised the tax on other tobacco products an equivalent amount. The initiative created the Cigarette and Tobacco Products Surtax Fund, consisting of six accounts in which specific percentages of the revenue are deposited annually (see Figure 2): the Research Account (5 percent), the Health Education Account (20 percent), the Hospital Services Account (35 percent), the Physician Services Account (10 percent), the Public Resources

Account (5 percent), and the Unallocated (or General Purposes) Account (25 percent). Collection of the tax began on January 1, 1989.

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

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



### **Scientific Advisory Committee**

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

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

TRDRP receives funding from the Proposition 99 Research Account. The California Department of Health Services (DHS) and the California Department of Education (CDE) receive funding from the Proposition 99 Health Education Account. During 2002, TRDRP staff worked with their counterparts from the DHS Tobacco Control Program and the CDE Tobacco Use Prevention Education program to keep abreast of developments in their respective programs,

avoid duplication of effort, share expertise, and provide input into the development of each program's goals. To this end, TRDRP conducted a workshop about the Community-Academic Research Awards at the Tobacco Control Program's Project Directors Meeting. The joint funding of School-Academic Research Awards by TRDRP and CDE marks the first time that state agencies have pooled their resources to optimize tobacco control efforts of common interest. TRDRP has had representatives from both DHS and CDE on the Scientific Advisory Committee in order to facilitate coordination between the state's tobacco research efforts, on the one hand, and its community-based and school-based tobacco control efforts, on the other hand.

## **RESULTS OF FUNDED RESEARCH**

This section highlights the research findings from grants that ended in 2003.

### Nicotine Dependence

#### **Proteins Involved in Nicotine Receptor Clustering**

**William G. Conroy, Ph.D.**

**University of California, San Diego**

This research found that nicotine receptors clustering at specific regions on neurons allow for the activation of a subset of receptors in the interior of the cell, which initiates a specific behavior. Thus, determining where nicotine receptors are positioned on the neuron can determine their role in the behavioral effects of nicotine. This research also identified the proteins responsible for the "positioning" of the nicotine receptors. While the specific proteins examined did not predict the precise grouping of the nicotine receptors, investigators found that the proteins probably interact with other cell adhesion molecules to determine the positioning of the nicotinic receptors. Results of the research offer neuroscience new insight into the molecular pathways and the long-lasting cellular changes that lead to and sustain nicotine addiction.

#### **Neurobiological Substrates of Nicotine Addiction**

**Athina Markou, Ph.D.**

**Scripps Research Institute**

This study sought to identify the level of nicotine exposure that results in larger and longer-lasting withdrawal effects. There were two major findings from this research. (1) Increases in the total nicotine dose resulted in increased overall severity of the affective aspects of withdrawal in animals. (2) Continuous exposure to nicotine resulted in longer-lasting withdrawal compared to intermittent nicotine intake, *even when the total dose of nicotine was the same*. In addition, extended exposure to nicotine in animals did not lead to escalation of self-administered nicotine intake, *but led to a decrease in nicotine intake*. This is unlike what occurs with extended access to cocaine. These findings imply that cessation practitioners must consider whether people are heavy (i.e., extended) smokers or intermittent smokers, since withdrawal effects for heavy smokers will be more severe. Conversely, addicted smokers may not increase the number of cigarettes smoked even if they have been smoking for years.

## **Role of Nicotine in Neuroprotection**

**Maryka Quik, Ph.D.**

**The Parkinson's Institute**

Epidemiology studies show that smokers have a lower incidence of Parkinson's disease than non-smokers. Thus, in contrast to the negative health effects generally associated with smoking, there seems to be some component in cigarettes that may protect against Parkinson's disease. Recent studies suggest that nicotine may be the active protective ingredient. These studies, conducted in animal models and cellular cultural medium, found that specific nicotine receptors (i.e., certain proteins in the brain) are critical in preventing neural damage. The identification of the specific receptors has spawned in-depth research by other investigators which was presented in a day-long symposium chaired by Dr. Quik at the 2003 annual meeting of the Society for Neuroscience.

## **Nicotine Dependence and Schizophrenia**

**Svetlana Semenova, Ph.D.**

**Scripps Research Institute**

Using an animal model, this research explored possible overlapping mechanisms underlying the negative symptoms of schizophrenia and nicotine withdrawal. Results showed that administration of the antipsychotic drug clozapine during nicotine withdrawal reversed the increased number of somatic signs of withdrawal, but had no effect on the affective aspects of nicotine withdrawal. However, treatment with clozapine before exposure to nicotine prevented the increase in somatic signs of withdrawal and also reduced the affective aspects of nicotine withdrawal. These findings are consistent with clinical data showing that clozapine treatment reduced smoking among schizophrenia patients. Nicotine also increased glutamate release (glutamate functions as a neurotransmitter that excites cells of the central nervous system) in schizophrenia patients, which normalized their attention processes. The results of these studies will have important implications about the treatment of nicotine withdrawal in psychiatric and non-psychiatric populations.

## **Contributions of CNRs to Nicotinic Signaling**

**Martina Blank, Ph.D.**

**University of California, San Diego**

This research sought to determine if a specific class of proteins on the surface of nerve cells, cadherin-related neuronal receptors (CNRs), regulates the formation of nicotinic synapses during development of the nervous system. The research identified two CNRs and demonstrated that their messenger RNA is expressed in a neuron-specific way. The research also established a new method to target neurons in live organisms, which can now be used to manipulate the proteins. Findings on the synaptic localization, the time course of expression, and the molecular interactions of these cell surface proteins suggest an important role in nicotinic synapse formation.

## Tobacco Use Prevention and Cessation

### **Lowering Smoking and Environmental Tobacco Smoke (ETS) Risks in Immigrant Pacific Rim Youth**

**C. Anderson Johnson, Ph.D.**

**University of Southern California**

Over four years, this project developed, tested, delivered and evaluated a multicultural smoking prevention curriculum for middle-school students that combined both distinctive and shared cultural features of Hispanic/Latino and Asian Pacific Islander cultures. Students from 24 schools in the greater Los Angeles basin participated in the study, with 8 schools receiving the multicultural curriculum, 8 schools receiving a culturally non-specific curriculum, and 8 schools serving as control sites. Of the ethnic groups who received the multicultural curriculum, Hispanic/Latino boys were found to be less likely to initiate smoking relative to other ethnic groups. The prevention effect among Hispanic boys is an important achievement, since 6<sup>th</sup> and 7<sup>th</sup> grade Hispanic/Latino boys are the most at risk for initiating smoking. As Hispanics/Latinos and Asian-Pacific Islanders comprise an increasing proportion of the adolescent population, the need for effective health education programs for these groups will grow correspondingly.

### **Telephone Counseling for Smokers Using Pharmacotherapy**

**Shu-Hong Zhu, Ph.D.**

**University of California, San Diego**

This study tested the effects of telephone counseling on smokers who use pharmacotherapy (nicotine patches, nicotine replacement therapy) for help with quitting smoking. 2,744 study participants were recruited through the Helpline, and then randomized them into 3 intervention groups that received either (1) minimal (materials only), (2) moderate (1 counseling session), or (3) comprehensive (6 sessions) telephone counseling. Initial results show that people using pharmacotherapy and received moderate or comprehensive telephone counseling had higher 90-day abstinence rates compared to the minimal intervention group who received materials only. While the differences between the minimal intervention (11.1%) and the moderate (16.4%) and comprehensive (16.5%) modalities were significant ( $p=.002$ ), the difference between the moderate and the comprehensive interventions was not significant. There appears to be no advantage to additional follow-up counseling for this population beyond the single pre-quit session. Dr. Zhu is continuing the data analysis from this research and preparing his findings for publication.

### **Dissemination of a Smoking Cessation Program for Inpatients**

**C. Barr Taylor, M.D.**

**Stanford University**

The aim of this study was to determine the effectiveness of implementation (by the research team) and institutionalization (by hospital staff) of a tobacco use cessation program for hospital inpatients, and the factors that affect outcome. The mean six-month self-reported cessation rates were 26% in the implementation phase compared with nearly 23% during the institutionalization phase. Hospitals with paid professionals providing the program had the best outcomes. Although fewer older individuals want to quit, they are more successful than younger smokers. Women had a worse six-month outcome than men (32% vs. 19%). This study demonstrated the effectiveness of a smoking cessation program offered to patients before they were admitted to the

hospital. Six months after completing the program, 25% of participants were abstinent. Active administrative support is critical for success of such a program.

### **School-based Anti-tobacco Programs for Deaf/Hard of Hearing Youth**

**Barbara Berman, Ph.D. and Debra-Sue Guthmann, Ed.D.**

**University of California, Los Angeles and California School for the Deaf, Fremont**

School-based tobacco prevention and cessation programs tailored to the unique social, cultural, educational and communication needs of deaf and hard-of-hearing (deaf/hh) children, adolescents and young adults do not currently exist. Through a school/academic collaboration, a school-based anti-tobacco curriculum for deaf/hh youth was developed, tested in focus groups of students, faculty/staff, and parents, and reviewed by educators and community leaders serving the deaf community. A randomized controlled trial is now being conducted to test the curriculum.

### **Prescription for Change**

**Karen S. Hudmon, Dr. P.H.**

**University of California, San Francisco**

This research produced and disseminated *Rx for Change*, a comprehensive tobacco use cessation training program/curriculum for students in the health professions generally and in schools of pharmacy particularly. The curriculum was adapted for use in schools of nursing and dentistry. The nine-week curriculum covers the impact of tobacco use and nicotine addiction on the body and the latest cessation methodologies. *Rx for Change* is now a required course work at all four California schools of pharmacy and at the UCSF School of Medicine. Dr. Hudmon has successfully leveraged her TRDRP grant for funding from the National Institutes of Health, thus ensuring the nationwide impact of this project. Already, the National Cancer Institute is conducting a 14-community study of licensed physicians and pharmacists in Texas using the *Rx for Change*.

### **RCT of Tobacco Dependence Treatment Benefits in HMOs and PPOs**

**Helen Halpin Schauffler, Ph.D.**

**University of California, Berkeley**

This study assessed the impact of offering full health coverage for different smoking cessation treatments with smokers enrolled in Blue Shield of California's individual and family PPO plans. Participants were randomly assigned to one of three treatment groups: 1) coverage for proactive telephone counseling and pharmacotherapy conditional on enrollment in the counseling program, 2) coverage for pharmacotherapy (unconditional) and telephone counseling, 3) coverage for pharmacotherapy alone. Results showed no differences among the groups in sustained quit rates, but those who used the benefits had significantly higher rates of quit attempts and quit rates for seven or more days than those who did not. The only factor that predicted sustained quit rates was enrollment in telephone counseling, and those in the group with linked benefits were significantly more likely to enroll in the telephone counseling program. The findings have direct policy relevance for increasing access to nicotine dependence treatments for California's insured population who receive their health care through PPOs.

## **A Longitudinal Study of Smoking Transitions in Youth**

**Elizabeth Gilpin, M.S.**

**University of California, San Diego**

This study involved a third follow-up of young adults first interviewed in 1993 as 12- to-15-year olds, and interviewed again in 1996 as 15- to 18-year olds. Overall, 44% (2,445) of the original 1993 sample was interviewed all three times. “Never smokers” at baseline who were receptive to tobacco industry advertising and promotions had an increased likelihood of being a current established smoker as a young adult compared with those who were not receptive during adolescence. Transitions from “committed never smoker” to “experimenting” were significantly lower in the later cohort when cigarette prices were higher than for the earlier cohort. Those with home smoking bans in both 1993 and 1999 were less likely to be current smokers in 1999. Both college students and non-students subject to workplace smoking bans showed similar lower smoking prevalence. In other settings (not employed or working where there were not complete smoking bans), students showed lower levels of smoking prevalence. In sum, tobacco advertising and promotions are implicated in recruiting adolescents to be adults smoker; cigarette price may have led to the decline in transitions toward smoking; and smoking bans appear to discourage young adult smoking.

## **Economic and Financial Analysis of Smoking Cessation Therapies**

**James M. Lightwood, Ph.D.**

**University of California, San Francisco**

The total annual cost of medical services attributable to smoking is \$50 billion, with another \$50 billion in lost wages. This project estimated the direct medical cost savings for the health care industry for adults who quit smoking, up to death or entry into Medicare (age 18 to 64). Savings were calculated for the 16 leading causes of death and illness attributable to smoking in men and women in this age group, including maternal complications and low birth weight for women. The estimates were calculated for both lifelong smokers and “typical” smokers who may quit later in life, taking into account the change in overall death rate following cessation.

<b>Lifelong Smokers</b>	<b>Cost Savings</b>	<b>Typical Smokers</b>	<b>Cost Savings</b>
Women, 18-39	\$ 6,200	Women 18-39	\$ 3,600
Women, 40-64	\$ 5,800	Women 40-64	\$ 3,900
Men, 18-39	\$ 8,000	Men 18-39	\$ 4,700
Men, 40-64	\$ 8,000	Men 40-64	\$ 5,300

The undiscounted costs ranged from \$4,700 to \$19,000. The results from this project have been used to estimate the net cost/benefit to health care plans and employers of providing smoking cessation therapies. That analysis showed that individual health care plans can provide a significant level of health-professional smoking cessation counseling free of charge and still save money, and that pharmaceutical therapies can be provided at a discount to enrollees.

**Economic Analysis of Factors Influencing Teen Smoking**  
**Sherry L. Emery, Ph.D.**  
**University of California, San Diego**

This is the first study to specifically examine the extent to which cigarette prices affect rates of smoking and smoking initiation among adolescents (i.e., price elasticity of demand). Over 80% of teens who smoke do not buy their own cigarettes, but instead obtain them from friends or other social sources. In addition, current and established smoking status and conditional demand were both sensitive to cigarette prices, suggesting that established adolescent smokers are highly sensitive to cigarette prices. The preliminary conclusions are that higher excise taxes may not deter experimentation, but appear to play an important role in discouraging regular smoking. Higher taxes may also reduce the number of cigarettes smoked and therefore deter progression to established smoking for adolescents.

**Natural History of Tobacco Addiction in Adolescents**  
**Anna-Barbara Moscicki, M.D.**  
**University of California, San Francisco**

This research surveyed 2,083 9<sup>th</sup> graders from 7 San Francisco Bay Area high schools about their use of tobacco, and also collected saliva cotinine samples to verify self-reports of non-smoking. The sample was multiracial/multiethnic, including Latino, Asian, Caucasian, African American, and Pacific Islander, Native American, and mixed. The first follow-up survey of 1,229 adolescents determined that 17.8% were smokers and 10% were ex-smokers. The final follow-up survey of 1,021 students during the 11<sup>th</sup> grade year of this cohort found that 25% were now current smokers. Compared with non-daily smokers, daily smokers had more expectations that smoking will reduce negative affect and boredom, enhance stimulation and help with weight control. Among adolescents who had never smoked at baseline, recognition of cigarette brand by advertising, willingness to wear tobacco-branded products, stress and having friends who smoked were significant predictors of intention to smoke and smoking initiation. No racial or ethnic differences were found. This research also confirmed that the newly modified Fagerstrom Tolerance and Nicotine Dependence Scale (FTND) and the Nicotine Dependence Syndrome Scale (NDSS) were able to accurately identify adolescents who became daily smokers. Findings from this study were published in the scientific literature.

**Tobacco Control Policy**

**Persistent Smoking in Bars: An Ethnographic Analysis**  
**Roland Moore, Ph.D.**  
**Pacific Institute for Research and Evaluation**

This study sought to understand how and why many stand-alone bars (not connected to restaurants) in San Francisco are not complying with California Assembly Bill 13, the Smoke Free Workplace Ordinance. Surveys and observations in 60 randomly selected bars revealed that half (50.4%) of the bars fully complied with the law, other bars were in transition from smoking to non-smoking, and a minority (14.9%) of bars remained non-compliant. Smoking was endemic in bars that cater to Asian and Irish patrons. Staff smoking was highly predictive of patron smoking, suggesting that, to some extent, bartenders model and control patron behavior. Observations and interviews with bartenders indicate the degree to which bar culture has

changed in response to the smoke-free bar ordinance: bar patrons and staff in compliant bars “just got used to” not smoking in bars.

### **Model for Surveillance of California Tobacco Control Policies**

**Harold Holder, Ph.D.**

**Pacific Institute for Research and Evaluation**

This project created a state-level computer simulation model—CaISim—similar to the national SimSmoke model. CaISim can be used to better understand the impact of public policies on smoking to health, including effects on particular age, gender and racial/ethnic groups. The California model can be used by legislators, health workers, enforcement agencies and others to predict smoking rates and tobacco-related deaths, and to understand the effects of specific policies on smoking rates and smoking-related death. For example, the model can be used by policy makers to estimate the long-term impact of a tax increase on smoking rates or deaths, and to compare these effects to those of youth access policies alone or in combination with tax policies. The model also can be used as an educational tool to demonstrate the effects of tobacco control policies on public health.

### **The Role of Media in Smoking Initiation and Cessation**

**David M. Burns, M.D.**

**University of California, San Diego**

Using a cigarette advertising database and cigarette sales data, the project examined the temporal relationship between the advertising and sales of the top 20 advertised low-tar brands between 1960 and 1996. Low-tar brand extensions such as Marlboro Light and Camel Light saw a steady increase in advertising between 1969 and 1974, but dramatic increases in sales for these brands did not occur until 1975. The proportion of advertising and sales for low-tar product extensions rose more sharply than the advertising and sales for stand-alone low-tar brands, suggesting it may have been easier to get smokers to switch to low-tar extensions than it was to get smokers to try new low-tar brands. It is also likely that the heavy advertising of low-tar cigarettes during the mid-1970s and early 1980s resulted in many smokers switching to low-yield brands rather than quitting smoking. Advertisements with themes that describe people or activities pictured in the advertisement, and themes related to smokers’ economic concerns were more likely to appear in ads for mentholated brands, which are preferred by African Americans, than brands preferred by whites. Themes related to the smoker’s health were no more likely to appear in ads favored by African Americans than those preferred by whites.

### **Dissuading At-risk Youths from Smoking via Mass Media**

**Cornelia Pechmann, Ph.D.**

**University of California, Irvine**

The effect of antismoking ads in nine categories (Disease and Death, Addiction, Dying Parent, Secondhand Smoke, Cosmetics, Acceptance of Nonsmokers, Marketing Tactics, Youth Activism, and Selling Disease and Death) was tested with school-aged youth. Their prior smoking behavior as well as personality traits associated with smoking including aggression, anxiety, delinquency, depression, sensation seeking, and self-esteem were also measured. Only the Disease and Death ads and Addiction ads lowered intent to smoke among moderate risk youth who had tried smoking but were not delinquent. Delinquent youth were unaffected by the ads. A second component of this research tested two opposing theories—Social Conformity

Theory and Social Projection Theory—on adolescents’ responses to the depiction of smoking in youth-oriented TV shows. Data from this component are being analyzed.

### **Tests of the Tobacco Industry’s Youth Smoking Prevention Ads**

**Stephen Fortmann, M.D.**

**Stanford Center for Research in Disease Prevention**

Study 1 found that exposure to Philip Morris’ youth smoking prevention campaign significantly improved the sponsor’s image as much as the advertising campaign that features the company’s contributions to charitable causes. Study 2 demonstrated that California’s anti-industry ads inoculated young adults against corporate image and youth smoking prevention ads sponsored by Philip Morris only among those viewers who were unaware that Philip Morris is a tobacco company. Study 3 found that, although adolescents’ intention to smoke did not differ as a function of ad exposure, youth smoking prevention ads sponsored by Philip Morris and Lorillard were more pro-industry than anti-smoking.

### **Evaluation of Office Environmental Tobacco Smoke (ETS) Exposure in Relation to AB13**

**Leon E. Alevantis, M.S. and William J. Fisk, M.S.**

**Public Health Institute and Lawrence Berkeley National Laboratory**

This research evaluated the effects of various design-, ventilation-, and operation-related variables on smoking room performance, and developed a mathematical model to predict performance of smoking rooms under various design and operating conditions. Data from the 1999 California Tobacco Survey (CTS) and the 2000 and 2001 California Adult Tobacco Survey (CATS) indicate that between 120,000 and 170,000 adult non-smokers work in buildings that have designated smoking rooms, and that between 270,000 and 330,000 adult non-smokers work in buildings where smoking is allowed indoors in locations other than designated smoking rooms, which is a clear violation of the law. Multiple laboratory experiments conducted in a simulated smoking room demonstrated the need to maintain a depressurized environment to ensure little ETS leakage to the non-smoking areas. Replacing the normal swinging door with a sliding door reduced the ETS leakage during periods of door opening by almost 80%. A model based on mass balance, exhaust flows, and pressure gradients was used to predict room performance for 23 of the chamber tests. These results have been presented to the committee that is revising the standards on ventilation and indoor air quality within the American Society of Heating, Refrigerating, and Air Conditioning Engineers.

### **Tobacco Control Digital Library**

**Karen Butter, M.L.**

**University of California, San Francisco**

The University of California, San Francisco Library has become a global resource for tobacco control information and tobacco industry documents. There are now more than 37 million tobacco industry documents on the Tobacco Control Archives website. Previously unavailable collections were added to the Archives and a new website merging a number of separate document collections was developed. The processing and description of tobacco industry documents was also standardized, which will improve access to the documents’ contents. The tobacco industry documents have resulted in more than 77 peer-reviewed, scholarly publications by researchers around the world.

## Cancer

### **Detection of Occult Metastasis in Patients with Lung Cancer**

**Richard J. Cote, M.D.**

**University of Southern California**

Surgery, alone or in combination with chemotherapy, remains the only available treatment for lung cancer. However, treatment often fails because the disease is diagnosed after the cancer cells have spread (metastasized) to other parts of the body. This project developed innovative methods to detect these earliest rare metastatic cells (occult metastases). Findings revealed that patients who have positive lymph nodes are a distinct population from those who are bone marrow positive. These findings have provided preliminary data that resulted in a grant from the National Cancer Institute to continue this research.

### **Testing Chemotherapeutic Strategies Against Lung Cancer Recurrence**

**Jenny Mao, M.D.**

**University of California, Los Angeles**

The overproduction of prostaglandin E2 (PGE2) is considered to be a driving force underlying lung cancer development. This clinical study found that an oral non-steroidal anti-inflammatory drug, Celebrex, modulated PGE2 production in cancer-free heavy smokers. These results suggest that Celebrex warrants continued evaluation as a preventive agent in heavy smokers. The study provided preliminary data for a grant from the National Cancer Institute.

### **Computerized Tomography (CT) Imaging to Assist Diagnosis of Solitary Pulmonary Nodules**

**Michael McNitt-Gray, Ph.D.**

**University of California, Los Angeles**

Computerized tomography (CT) is a sophisticated imaging technology that is increasingly being used to identify lung cancer early in the disease process. As with any sensitive diagnostic tool, there is a certain probability of false positives (i.e., pulmonary nodules identified as cancerous but which are actually benign). This project was part of a concerted effort to develop approaches to discern benign from malignant nodules using statistical and pattern recognition techniques and parameters such as size, shape, density, density distribution, contrast injection enhancement and texture.

### **Overcoming Drug Resistance in Small Cell Lung Cancer**

**Kristina Vuori, M.D., Ph.D.**

**The Burnham Institute**

Most patients with small cell lung cancer initially respond well to chemotherapy, but the cancer almost invariably relapses and becomes resistant to treatment. The research showed that integrins (cell surface molecules which normally anchor cells in place), dysfunction in cancer and actually inhibit the cells from self-destructing, thus protecting cancerous cells from the effects of chemotherapy. The research also showed that antibodies that bind to the specific integrins involved in this response increased cellular resistance to chemotherapeutic agents, and identified a crucial enzyme involved in chemotherapeutic resistance.

**DNA Replication, Regulation of the Cell Cycle, and Cancer**  
**Judith Campbell, Ph.D.**  
**California Institute of Technology**

To understand the mechanisms involved in the regulation of cell proliferation and its loss in cancer, it is crucial to know how the cell cycle is regulated. This research focused on the role of Cdc6p, an important protein in one phase of the cell cycle. A model was developed showing a central role for Cdc6 in coordinating the cell cycle, in addition to its role in the initiation of DNA replication. The results of several experiments validated this model.

**Regulation of the MAP Kinase Pathway by CAMP in Lung Cancer**  
**Renate Pilz, M.D.**  
**University of California, San Diego**

About 80% of non-small cell and most of small-cell lung cancers are attributable to smoking. The mitogen-activated protein kinase (MAPK) pathway is involved in the regulation of cell growth, differentiation, and death of both small cell and non-small cell lung cancers. It is important to understand better MAPK pathway regulation in lung cancer because drugs to inhibit this pathway are being developed and tested in clinical trials. Analogs of particular enzymes that regulate metabolic reactions (i.e., cyclic AMP-dependent protein kinase or CAMP) inhibited MAPK activity in non-small cell lung cancer, but increased activity in small cell lung cancer. The growth inhibitory effects of CAMP on lung cancer cells varied across the CAMP analogs.

Heart Disease

**Tobacco Exposure and Subclinical Atherosclerosis in Non-Insulin Dependent Diabetes Mellitus**  
**Wendy Mack, Ph.D.**  
**University of Southern California**

Atherosclerosis and cardiovascular-related events are the primary cause of morbidity and mortality in persons with diabetes. This project used data from a clinical trial conducted among 299 adults (91% Hispanic) with non-insulin dependent diabetes mellitus (NIDDM, or type 2 diabetes) to evaluate the association between active smoking and exposure to secondhand smoke (SHS) and atherosclerosis. Atherosclerosis was measured by carotid artery wall thickness (intima media thickness or IMT). At baseline, the major contributors to IMT were smoking, total cholesterol, and systolic blood pressure, and thicker IMT was observed in diabetic smokers compared to those with diabetes who had never smoked. IMT increased with greater duration and frequency of smoking. There was no difference in IMT between former and current smokers, and in former smokers there was no relationship between years since quitting smoking and IMT. The negative effects of smoking were greater among those who had had diabetes longer, suggesting an interaction between the diabetes process and smoking on atherosclerosis. SHS exposure at home and work was not significantly related to IMT measured at baseline or to the progression of IMT measured over the 2-year follow-up. In contrast, persons who reported exposure to SHS at places outside of home and work had a significantly greater IMT progression rate measured over the 2-year follow-up than persons not exposed to SHS from this source.

## **Mentholated Cigarettes and Risk of Acute Myocardial Infarction, Coronary Heart Disease, and Stroke**

**Stephen Sidney, M.D.**

**Kaiser Foundation Research Institute**

This research investigated whether smoking mentholated cigarettes increases the risk of acute myocardial infarction (heart attack), coronary heart disease, and stroke using a retrospective cohort study among 83,276 members of the Kaiser Permanente Medical Care Program, Northern California region. Although there was no difference in the risk of hospitalization between smokers of mentholated and non-mentholated cigarettes, the risk of death from myocardial infarction was 31% lower in mentholated than in non-mentholated cigarette smokers. Conversely, the risk of death from stroke was 24% higher in mentholated than in non-mentholated cigarette smokers, but this result did not achieve statistical significance.

## **Macrophage Function in Atherosclerosis**

**Linda K. Curtiss, Ph.D.**

**The Scripps Research Institute**

Atherosclerosis (hardening of the artery wall) is thought to be a result of a chronic inflammatory condition involving the entry of macrophages into the susceptible arteries, retention of these macrophages within the layer where they cause disease progression, and subsequent accumulation of lipids within the lesions or plaques. Tobacco use accelerates the development of atherosclerosis. This research used bone marrow transplantation in mice to identify the role of a particular cell receptor, CXCR2, in retaining macrophages within lesions in the artery. Results confirmed that mice transplanted with CXCR2 bone marrow have less atherosclerosis and fewer macrophages.

## **Diagnostic Tools of High Density Lipoprotein (HDL) Damage by Tobacco Smoke**

**John K. Bielicki, Ph.D.**

**Lawrence Berkeley National Laboratory**

Cigarette smoking is an independent risk factor for the development of heart disease, including atherosclerosis (hardening of the artery wall). Elevated levels of the high density lipoprotein (HDL) – known as the “good cholesterol” – are associated with reduced risk of atherosclerosis and protection of the artery wall from oxidative damage and depositing of cholesterol. This research provided evidence for one mechanism by which cigarette smoke reduces HDL levels in smokers. One component of the HDL is the enzyme lecithin:cholesterol acyltransferase (LCAT) which facilitates the removal of cholesterol from arteries. Gas-phase cigarette smoke produces a rapid inactivation of LCAT catalytic activity. Antibodies against native and modified LCAT forms were created. These antibodies have important diagnostic value for determining whether oxidative stress incurred upon exposure to cigarette smoke modifies LCAT and inhibits its function. Thus the antibodies have clinical applications for predicting HDL deficiency.

## **Integrins in Sympathetic Innervation of the Heart**

**Dennis Clegg, Ph.D.**

**University of California, Santa Barbara**

Sympathetic neurons convey stress signals from the brain to the heart and blood vessels, resulting in an increased pulse and increased blood pressure. This relay system functions in the

“fight or flight” response that allows animals to take action in times of stress. However, excess stimulation of the sympathetic nerves can lead to hypertension, an arrhythmic heartbeat and heart attacks. Smoking may contribute to heart disease via long term stimulation of the sympathetic innervation of heart muscle and blood vessels. This research mapped the interaction of two proteins that maintain the innervation of the heart, which may lead to strategies to treat heart disease associated with smoking.

### **Carbon Monoxide as a Modulator of Myocardial Function**

**Ulrike Kreutzer, Ph.D.**

**University of California, Davis**

Carbon monoxide (CO) is a deadly poison in environmental tobacco smoke (ETS), but the precise cellular damage remains an open question. Too much CO displaces oxygen in the blood, and the cells suffocate. Although the CO level in ETS is low, the reduced oxygen delivery still compromises cardiac function. Even at low concentration, CO can bind tightly to the intracellular oxygen-storage protein myoglobin (Mb) as it does to oxygen-carrying protein hemoglobin (Hb) in the red blood cells. This research investigated the role of Mb in cellular oxygen transport. Even under increased workload and oxygen demand, inhibition of Mb’s oxygen-carrying capacity did not impact heart performance or bio-energetic parameters. These data suggest that acute Mb inhibition with CO indeed produces an alteration in cellular metabolism but does not impair heart function, even during enhanced demand.

### **Nicotine Regulates Cardiac Toxicity with Lipopolysaccharide**

**Wilbur Lew, M.D.**

**University of California, San Diego**

This research evaluated whether nicotine inhibits a unique form of cell death (i.e., apoptosis) in the heart and thus have a protective effect. Rats that were pretreated with nicotine and injected with lipopolysaccharide (LPS), a component of common forms of bacteria, suffered no heart damage. Rats that were pretreated with a placebo, however, showed increased cell death. Further experiments showed that nicotine also acts directly on heart muscle to protect against apoptosis. These findings offer potential for the application of nicotine to prevent injury to the heart from apoptosis during procedures or conditions associated with temporary increases in LPS in the blood.

### **Smoking and Virulence of Periodontal Pathogens**

**Hansel M. Fletcher, Ph.D.**

**Loma Linda University**

In the United States, over 49 million people are affected by the gum disease, periodontitis. Cigarette smoking worsens the gum disease and increases the risk for cardiovascular disease. The research found that the most significant enzymes from the bacterium *Porphyromonas gingivalis* worsen periodontitis by killing blood vessel cells. Cigarette smoke – including secondhand smoke – enhanced the ability of the enzymes to kill the cells. Cigarette smoke increased the release of enzymes from this bacterium, allowing bacteria to enter the blood stream and subsequently cause heart disease. These results confirmed that smoking can modulate the immune response and enhance infection-induced damage.

## Lung Disease

### **Lung Volume Reduction Surgery in an Animal Emphysema Model**

**Matthew Brenner, M.D.**

**University of California, Irvine**

Surgical removal of non-functional lung tissue (lung volume reduction surgery) can improve breathing function and alleviate symptoms like severe shortness of breath experienced by COPD (Chronic Pulmonary Obstructive Disease) patients. This project explored techniques to improve surgical outcome, such as parameters of lung function which are the best indicators for the amount of tissue to remove, which surgical techniques offer the greatest benefit and lowest risks to the patient, and the difference between short-term and long-term benefits. Methods were developed to optimize surgical success, and a new vacuum-assisted method was developed that provides a reversible means for reducing lung volume. This information will help develop lung volume reduction surgery as a more viable option for alleviating symptoms of respiratory distress in patients with severe COPD.

### **Human Tryptase Gene Expression: Role in Chronic Obstructive Pulmonary Disease (COPD)**

**George H. Caughey, M.D.**

**University of California, San Francisco**

One unanswered question in the field of smoking-related pulmonary disease is why some individuals are more disease-susceptible than others even though they have the same lifetime smoke exposure. Tryptases are enzymes released by the lung and airways cells in response to cigarette smoke which are believed to provoke and prolong inflammation. Investigators found inherited deficiencies in the common “alpha” form of this enzyme. Individuals who lack alpha-tryptase inherit instead the more active and pro-inflammatory “beta” form, and may therefore be more prone to smoking-related lung disorders such as asthma and chronic obstructive pulmonary disease. The research discovered substantial variation among ethnic groups in the form of tryptase that is inherited, which may explain some of the ethnic differences in response to cigarette smoke. The investigators also discovered a new gene product, pancreasin, which is produced by cells lining the airways and which is acutely expressed in bronchitis.

### **Skeletal Muscle Structure and Function in Chronic Obstructive Pulmonary Disease (COPD)**

**Timothy R. Gavin, Ph.D.**

**University of California, San Diego**

Although pulmonary rehabilitation is a critical component of treatment for chronic obstructive pulmonary disease (COPD), COPD patients typically find physical activity difficult or impossible. This project demonstrated for the first time that COPD patients have impaired skeletal muscle efficiency. Awareness of this previously unknown aspect of COPD will help researchers develop improved physical rehabilitation strategies to help COPD patients maintain and regain physical capabilities and thus improve their quality of life.

### **Chronic Bronchitis: Pathology of Mucin Gene Expression**

**Walter Finkbeiner, M.D., Ph.D.**

**University of California, San Francisco**

Chronic bronchitis – a condition of excess production of mucus in the bronchial tree – is one of the primary lung diseases caused by tobacco smoking. Normally, mucus acts to protect the lung from infection and injury, but in excess it can lead to pneumonia and airflow obstruction. Mucins make up a large part of mucus. This research developed improved methods for detecting lung mucin genes, and found that two important mucins (MUC5A and MUC5B) are altered by smoking. Larger amounts of these mucins were found in tissues of smokers and patients with chronic bronchitis than in the tissue of nonsmokers. This finding may lead to specific targets for drug therapy.

### **MCP1 and TGF-beta in Pulmonary Emphysema**

**David Morris, M.D.**

**University of California, San Francisco**

Using genetically engineered mice, this research discovered that TGF-beta (transforming growth factor beta), a protein involved in regulating lung structure, and MCP1 (macrophage chemoattractant factor), a regulator of the inflammatory response, are also involved in the regulation of lung surfactant components. Mice unable to express these proteins had irregularities in their surfactant composition and exhibited features of lung disease. Experiments were initiated to explore the feasibility of using TGF-beta to prevent smoke-induced lung damage.

### **Regulation of Lung Inflammation by the LTC4 Synthase Pathway**

**Kenneth Serio, M.D.**

**University of California, San Diego**

Bacterial infection in combination with smoke exposure is closely associated with the development of chronic obstructive pulmonary disease (COPD). This project investigated the enzyme regulation of leukotriene synthesis, which may function to protect the lung against bacterial infection. It was found that a key enzyme in this pathway, LTC4 synthase, is turned on by proteins normally present in inflammatory cells but is turned off by products released by bacteria. Such a response may allow bacteria to evade the immune system and become established in the lung. Not only does smoke exposure predispose the lungs to bacterial infection, but the bacteria can actually weaken immune defenses. This phenomenon may explain the prolonged and intensified inflammatory response observed in patients with COPD and asthma.

### **Environmental Tobacco Smoke Effects on Lung Surfactant**

**Joseph Zasadzinski, Ph.D.**

**University of California, Santa Barbara**

The first lung component exposed to smoke is the fluid lining of the epithelial cells, a complex mixture of surfactants and antioxidants. Surfactants minimize the work of breathing by reducing surface tension. Antioxidants protect against damage from noxious stimuli such as smoke. Using an elegant *in vitro* model, this research showed that environmental tobacco smoke

adversely alters the physico-chemical properties of lung surfactants. These results offer new insights into the inflammation and edema that are characteristic of asthma and bronchitis.

### **Molecular Targets for Tobacco Oxidants in Lung Cell Death**

**Tommer Ravid, Ph.D.**

**University of California, Davis**

There is evidence that the abundant reactive oxidants in cigarette smoke play a role in cigarette smoke-induced adverse health consequences, presumably when the oxidants are absorbed and affect lung epithelial cell function. This research identified major elements in the apoptosis (a form of cell death) of lung epithelial cells during oxidative stress, and suggested an order for the apoptotic events. The outcome of this study will shed light on our understanding of the mechanisms by which lung cells perceive, discriminate, and respond to oxidative stress, and will determine how specific molecular targets contribute to lung injury.

### **Tobacco Oxidants in the Ceramide Path and Lung Cell Death**

**Tzipora Goldkorn, Ph.D.**

**University of California, Davis**

Cigarette smoke contains free radical and reactive oxidant species (ROS) that play a role in cigarette smoke-induced illness. This research found that exposure of epithelial cells in the lung to oxidative stress from one ROS, hydrogen peroxide, induces cell death. Ceramide is another messenger of cell death, and oxidative stress generated by hydrogen peroxide enhances ceramide generation.

## Effects on Reproductive Processes and Tobacco-Related Disease

### **Role of Passive Smoke on Intracytoplasmic Sperm Injection and In Vitro Fertilization**

**Hillary Klonoff-Cohen, Ph.D.**

**University of California, San Diego**

Intracytoplasmic sperm injection (ICSI) is an assisted reproductive technology procedure which consists of *in vitro* fertilization accomplished by injecting a single sperm directly into the egg. Lifestyle factors may play an important role on ICSI success rates and pregnancy outcomes. This research examined the effects of direct and passive tobacco smoke on a sample of 200 infertile men undergoing ICSI on reproductive endpoints (fertilization, implantation, embryo transfer, and pregnancy outcome). Preliminary findings with a sub-sample of 52 men revealed a trend for men who smoked cigarettes within the past year or past six months and decreased pregnancy rates. There was twice the risk for an unsuccessful pregnancy after undergoing ICSI for infertile men who smoked cigarettes within one year of the procedure compared to non-smokers. In addition, there was also a statistically significant effect for cigar use within the past year and unsuccessful pregnancies. If these findings are replicated on the entire sample, it may be advisable for men to abstain from smoking cigarettes and cigars for one year before attempting to undergo ICSI.

### **Ascertainment of Environmental Exposure During Pregnancy**

**Martin Kharrazi, Ph.D.**

**Sequoia Foundation**

This research described the pattern of exposure to tobacco smoke across the course of pregnancy, and tested the accuracy of a smoking behavior question for inclusion in the next version of the California Birth Certificate. Blood and urine samples from nearly 3,000 pregnant women are being analyzed for the presence of cotinine, a chemical produced when nicotine is metabolized. The analysis will verify results of two smoking behavior questions asked of approximately 24,000 pregnant women who were in the hospital to deliver. Preliminary data on 7,000 questionnaires suggest that the New Smoking Question that asks the number of cigarettes smoked per day during 4 time periods is more accurate than the Old Smoking Question that asks the estimated number of cigarettes smoked during pregnancy. The results of the first question show that women's use of tobacco and exposure to other smokers declined during the pregnancy.

### **Modeling the Relation of Smoking to the Ovarian Function**

**Yan Liu, M.D.**

**University of California, Davis**

This study sought accurate estimates of the effect of smoking on the length and regularity of the menstrual cycle. This is a reflection of ovarian steroid production and women's exposure to steroid hormones before menopause may influence the development of various chronic diseases. Smoking was associated with a moderately increased risk of anovulation (the absence of ovulation), but secondhand smoke exposure was not. However, secondhand smoke exposure was related to an increased risk of long menstrual cycles (>35 days) and long follicular phases (>23 days). Further, smokers exhibited a less pronounced estrogen metabolite excretion at the mid-cycle as well as in the luteal phase; they also had a more pronounced progesterone metabolite excretion level during the entire menstrual cycle.

### **Effect of Nicotine on Fetal Hematopoietic Stem Cell Migration**

**Sophia Khaldoyanidi, M.D., Ph.D.**

**La Jolla Institute for Molecular Medicine**

The constituents of cigarette smoke, including nicotine, can cross the placental barrier and affect the development of the fetus in women who smoke during pregnancy. Previous experiments demonstrated that nicotine-exposed mice have a lower immune response. This research investigated the cellular and molecular mechanisms leading to lowering of the immune system after intrauterine exposure to nicotine. A series of experiments with nicotine-exposed mice showed that there is a decrease in lymphoid and stem cells in hematopoietic tissues (tissues where blood is formed) in the bone marrow. These findings suggest that nicotine affects the ability of hematopoietic stem cells to migrate from the fetal liver to the bone marrow during embryonic development.

### **Environmental Tobacco Smoke Exposure in the California Teachers Study Cohort**

**Peggy Reynolds, Ph.D.**

**Public Health Institute**

Researchers conducted a preliminary assessment of tobacco smoke and selected short-term chronic disease outcomes, including breast cancer, in a large (116,544), well-defined cohort of

female California professional school employees, a population with a low rate of current smoking and a high prevalence of never smoking. Current smokers tended to display characteristics more similar to passive smokers than to former smokers, highlighting the importance of separating former smokers from current smokers and removing passive smokers from the ‘unexposed’ group when examining the effects of active smoking on breast cancer. Further, the analysis of 2,005 cases of invasive breast cancer identified during the first five years of follow-up among cohort members without a history of breast cancer suggested an association of breast cancer with active, but not passive smoking.

### **Explaining the Inverse Smoking Association with Parkinson’s Disease**

**Lorene Nelson, Ph.D.**

**Stanford University**

Parkinson’s disease (PD) is one of a few conditions in which cigarette smoking appears to decrease the risk of developing the disease, with a reduced risk of 50% among ever smokers compared to never smokers. In this research, 496 patients with PD and 541 age- and gender-matched control subjects without PD were interviewed about use of tobacco, alcohol, caffeine and other substances. The DNA of study subjects was tested to identify genes that either increase or decrease the risk of developing PD. Current smokers or former smokers who had quit in the previous five years had a 70% reduction in the risk of PD compared to those who had never smoked. In addition, current drinkers of alcohol were at 60% reduced risk for PD, and those who consumed the highest quantities of caffeinated coffee or soda were also at reduced risk for developing PD. If the chemical agent(s) in cigarette smoke that protect(s) against Parkinson’s disease can be identified, methods of delivering that chemical could slow the progression of the disease.

### **Smoking and Depression in Chinese versus Non-Chinese**

**Janice Y. Tsoh, Ph.D.**

**University of California, San Francisco**

This study is the first to examine the relationship between smoking and depression in Chinese and non-Chinese smokers. Assessments of approximately 400 foreign- and American-born smokers in the San Francisco Bay Area were made at the study’s start and 6-months later. Chinese female smokers reported significantly elevated depression scores compared to Chinese males and compared to the non-Chinese sample. Male and female Chinese smokers were less aware of smoking cessation therapies (including nicotine replacement therapy, bupropion, hypnosis, and acupuncture) than were non-Chinese smokers. Interestingly, this research discovered that Chinese female smokers were less likely to be married compared to Chinese male smokers.

### **Cigarette Smoking in HIV-positive Populations**

**Gary L. Humfleet, Ph.D.**

**University of California, San Francisco**

Given the high smoking rate among HIV-positive patients and the negative effect of cigarette smoking on HIV-related medical conditions, this project sought to develop effective smoking treatments by investigating perceived barriers to treatment, preferred treatment elements, and preferred treatment settings. HIV-positive and HIV-negative gay male smokers did not differ on measures of nicotine dependence, current mood, and stress. Both reported high rates of major

depressive disorders and high levels of negative mood, particularly in comparison to a sample of male smokers from the general community. Both depression and negative mood are related to smoking treatment failure. In addition, HIV-positive men were significantly more likely to be ready to quit smoking than HIV-negative men. HIV-positive smokers identified smoking as a way to deal with stress and to cope with and prevent depression. Most were unaware of specific relationships between smoking and HIV illness. Many felt that quitting would have no impact on HIV illness; reported that medical professionals suggest quitting, but offer little support; and felt that treatments need to be intensive, convenient, and low cost.

### **PPARs in Intestinal and Colonic Tumorigenesis**

**Youngxu Wang, Ph.D.**

**The Salk Institute for Biological Studies**

Cigarette smoking, especially long-term continuous smoking, significantly increases the risk of colorectal cancer death in both men and women. Effective prevention or cure of this cancer requires a better understanding of the genes involved. A group of proteins named PPARs have been implicated, but their roles remain unclear. This research sought evidence of whether and how they are involved in colorectal cancer. Researchers found that activation of PPARs in mice has no effects on intestinal development, and mice showed no signs of tumor occurrence, suggesting that activation of these proteins alone is not sufficient to lead to the development of tumors.