



Annual Report

2006

Annual Report 2006

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

Charles L. Gruder, Ph.D.
Executive Director – Special Research Programs
Acting Director – Tobacco-Related Disease Research Program

Wyatt R. Hume, D.D.S., Ph.D.
Provost and Executive Vice President for Academic and Health Affairs

Tobacco-Related Disease Research Program
University of California, Office of the President
300 Lakeside Drive, 6th Floor
Oakland, CA 94612-3550

Phone: 510-987-9870
Fax: 510-835-4740
e-mail: trdrp@ucop.edu
www.trdrp.org

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EXECUTIVE SUMMARY

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

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

In 2006, 48 research grants were completed, representing cutting-edge science on tobacco-related disease and tobacco control policy and programs, particularly in those groups at highest risk for tobacco use and exposure to secondhand smoke. They include 10 on nicotine dependence, 5 on tobacco use prevention and cessation, 11 on tobacco control policy, 11 on cancer, 7 on heart and lung disease, and 4 on environmental tobacco smoke and effects of tobacco use on reproductive processes.

Brief summaries of the research findings, which appear at the end of this report, include:

- In an animal study, analgesia (reduced pain sensitivity) following exposure to cigarette smoke was prevented by mecamylamine (a nicotine receptor blocker) and naltrexone (an opiate receptor blocker), indicating that nicotine is critical to the pain-reducing effect of smoke exposure.
- Nicotine significantly enhanced memory in schizophrenics. This improvement in memory function, was greater than the changes documented by novel antipsychotic medications which are touted as having cognitive enhancing properties.

¹ <http://www.dhs.ca.gov/tobacco/documents/press/PressRelease04-10-06.pdf>

² Max, W. et al. The Cost of Smoking in California, December 2002.

- A classroom-based approach to teen smoking cessation found a a cessation effect on weekly smoking at posttest and two follow-up time points.
- A survey in San Diego, Tijuana, and Guadalajara found a positive association between the level of exposure to the California Tobacco Control Program and differences in smoking, smoking policies, secondhand smoke exposure, and theoretical determinants of smoking behavior.
- A mathematical model to estimate the public health effects of tobacco use showed that those who begin smoking as teenagers lose about 3.5 quality adjusted years of life between ages 18 and 70 in comparison to those who never smoked.
- California's comprehensive Tobacco Control Program has increased smoking cessation among young adults, compared with states which used cigarette excise taxes alone to discourage smoking or states with less well funded tobacco control programs.
- The finding that more than 56% of underage tobacco sales in Los Angeles occurred within 1,000 feet of a school was used by the Los Angeles City Attorney's Office to support new city legislation requiring tobacco vendors to register with the city and pay a yearly fee.
- A study of the impact of smoking cessation on the utilization and costs of medical care services for members in a large HMO in California found that the per person excess costs for current smokers, compared to never smokers, were \$413 for females and \$1,171 for males.
- Among smokers, African American grandparent caregivers were more likely to have a smoking-related disease than African American parents and non-African American parents and this was particularly true for cardiovascular disease.
- Compared to nonsmokers' cars, nicotine concentrations in smokers' cars were 4-7 times greater (dust), 10-24 times greater (surfaces), and 5-24 times greater (air).
- The first statewide random sample of Lesbian, Gay, and Bisexual households in California found that 28.7% of Lesbians, 26.9% of Bisexual women, and 43.6% of women who have sex with women were current smokers compared to 12.1% of women in general.
- In a randomized smoking cessation treatment study of enrollees in Blue Shield of California's Individual and Family PPO plans, the only factor predicting sustained quit rates was enrollment in telephone counseling.
- A study found that a particular gene combination (p53/p14ARF) was extremely potent at triggering tumor cell death through apoptosis and could therefore provide a highly effective, non-toxic biological therapy for lung cancer that exceeds the efficacy of current gene transfer vectors.
- Treatment of bladder cancer cells with rapamycin, an FDA-approved drug already in clinical trial for several forms of cancer, sensitized those cells to conventional chemotherapy, suggesting that rapamycin or its analogues could be combined with such therapies to improve patient response.
- A DNA-based vaccine administered together with cyclophosphamide, a drug often used for cancer chemotherapy, were far more effective in killing lung tumor cells and preventing their spread than either alone.

In 2006, TRDRP awarded \$14.5 million in 44 new grants (an additional 4 were declined) to scientists at 22 California non-profit research institutions. However, because of insufficient funds, TRDRP was unable to fund 47 research proposals that had been rated "outstanding" or "excellent" by expert peer reviewers, which was a three-fold increase over 2005.

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

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

INTRODUCTION

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

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OVERVIEW

Mission

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

Goals

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

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

¹ <http://www.dhs.ca.gov/tobacco/documents/press/PressRelease04-10-06.pdf>

² Max, W. et al. The Cost of Smoking in California, December 2002.

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

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

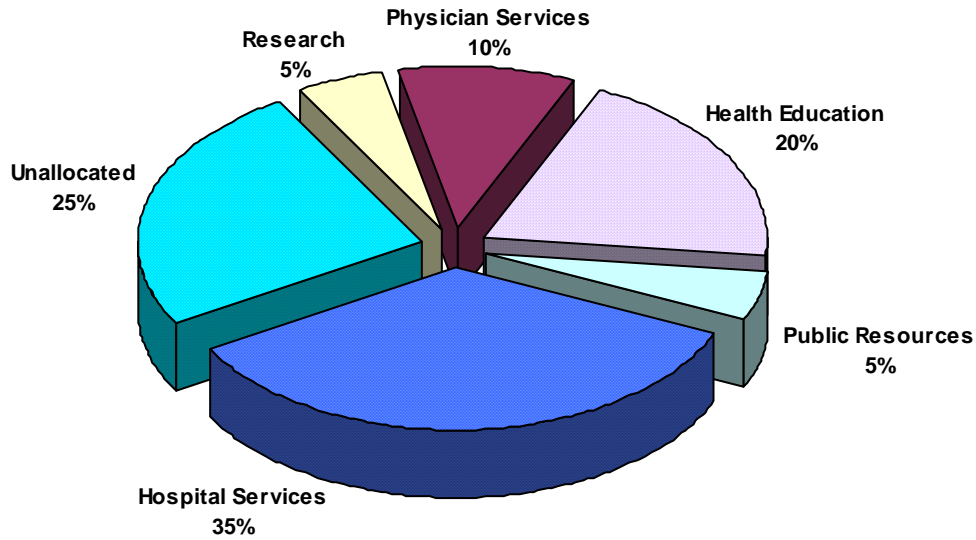
- Providing opportunities to researchers to conduct high quality and innovative research that advances tobacco-related science.
- Helping to build the research infrastructure in California that is critical for comprehensive tobacco-related disease research, in part by encouraging investigators to pursue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

Program Administration

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

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

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



REPORT ON 2006 ACTIVITIES

Completed Grants

In 2006, 48 research grants were completed, representing cutting-edge science on tobacco-related disease and tobacco control policy and programs, particularly in those groups at highest risk for tobacco use and exposure to secondhand smoke. They include 10 on nicotine dependence, 5 on tobacco use prevention and cessation, 11 on tobacco control policy, 11 on cancer, 7 on heart and lung disease, and 4 on environmental tobacco smoke and effects of tobacco use on reproductive processes.

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- A classroom-based approach to teen smoking cessation found a a cessation effect on weekly smoking at posttest and two follow-up time points.
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- California's comprehensive Tobacco Control Program has increased smoking cessation among young adults, compared with states which used cigarette excise taxes alone to discourage smoking or states with less well funded tobacco control programs.
- The finding that more than 56% of underage tobacco sales in Los Angeles occurred within 1,000 feet of a school was used by the Los Angeles City Attorney's Office to support new city legislation requiring tobacco vendors to register with the city and pay a yearly fee.
- A study of the impact of smoking cessation on the utilization and costs of medical care services for members in a large HMO in California found that the per person excess costs for current smokers, compared to never smokers, were \$413 for females and \$1,171 for males.
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- In a randomized smoking cessation treatment study of enrollees in Blue Shield of California's Individual and Family PPO plans, the only factor predicting sustained quit rates was enrollment in telephone counseling.
- A study found that a particular gene combination (p53/p14ARF) was extremely potent at triggering tumor cell death through apoptosis and could therefore provide a highly effective, non-toxic biological therapy for lung cancer that exceeds the efficacy of current gene transfer vectors.
- Treatment of bladder cancer cells with rapamycin, an FDA-approved drug already in clinical trial for several forms of cancer, sensitized those cells to conventional chemotherapy, suggesting that rapamycin or its analogues could be combined with such therapies to improve patient response.
- A DNA-based vaccine administered together with cyclophosphamide, a drug often used for cancer chemotherapy, were far more effective in killing lung tumor cells and preventing their spread than either alone.

Research Involving Women and Communities of Color

Of TRDRP's 190 active grants, 76 (40%) involve human subjects. Of the grants that involve human subjects, 73 (96.1%) involve both women and communities of color, 1 (1.3%) involves women but not communities of color, and 2 (2.6%) involve neither.

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

TRDRP coordinates its activities with the California Department of Health Services (DHS) and the California Department of Education (CDE) because the three agencies share the mission of reducing the harm and costs of tobacco use in the state. They receive funding from a common

source, the Cigarette and Tobacco Products Surtax Fund created by Proposition 99. During 2006, TRDRP staff continued to work with their counterparts from the DHS Tobacco Control Program and the CDE Safe and Healthy Kids Program Office to keep abreast of developments in their respective programs, avoid duplication of effort, share expertise, and provide input into the development of each program's goals. Following peer review, CDE and TRDRP jointly funded an evaluation of the "*I Decide* Teen Tobacco Cessation Program" which is being used in a number of California school districts.

Dissemination of Research Findings

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

• Scientific Publications

TRDRP-funded investigators have continued to actively disseminate findings from their research in scholarly publications and at scientific conferences. In 2006, funded investigators reported publishing 199 articles in refereed scientific journals, including 177 that had appeared in print and 22 that were accepted for publication and were awaiting appearance in print. Some of the peer-reviewed scientific journals in which the papers appeared include: *Addictive Behaviors*; *American Journal of Public Health*; *American Journal of Respiratory & Critical Care Medicine*; *Atherosclerosis, Thrombosis, and Vascular Biology*; *Biology of Reproduction*; *Birth Defects Research*; *Cancer Epidemiology, Biomarkers, and Prevention*; *Cancer Research*; *Cell Cycle*; *Chest*; *Circulation*; *Clinical Cancer Research*; *Environmental Science and Technology*; *FASEB Journal*; *FEBS Journal*; *Health Psychology*; *Immunology*; *Journal of Adolescent Health*; *Journal of Biological Chemistry*; *Journal of Clinical Endocrinology and Metabolism*; *Journal of Immunology*; *Journal of Neuroscience Molecular Biology of the Cell*; *Molecular Cancer Research*; *Nature Medicine*; *Nicotine and Tobacco Research*; *Oncogene*; *Preventive Medicine*; *Proceedings of the National Academy of Sciences USA*; *Psychopharmacology*; *Science*; *Stroke*; *Tobacco Control*; *Vascular Medicine*.

• Biennial Scientific Conference 2007

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

Approximately 300 researchers and tobacco control professionals are expected to attend TRDRP's Biennial Conference in Sacramento on October 8-9, 2007. The conference theme is "Future Research Opportunities." The keynote speaker in the opening session will be David Kessler, M.D., Dean of the School of Medicine and Vice Chancellor for Medical Affairs at the

University of California, San Francisco and former FDA Commissioner. The luncheon speaker will be Bill Lockyer, California State Treasurer and former California Attorney General. The plenary session will include talks on future research opportunities in developing nicotine vaccines, reducing health disparities, and pharmacogenomics.

- **Newsletter**

In 2006, TRDRP published two issues of its newsletter, *Burning Issues*, which contained articles on critical research topics in tobacco-related disease and tobacco use, and information about the program and notices of upcoming events. They included articles on the health effects of secondhand smoke exposure, the development of nicotine vaccines as smoking cessation treatments, and the rapid growth of hookah use. The newsletters are available on TRDRP's Web site, <http://www.trdrp.org/publications/Newsletters.asp>.

- **Web site**

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

2006 FUNDING CYCLE

- **Research Grants Awarded**

In 2006, TRDRP awarded \$14.2 million in 44 new grants to scientists at 15 California non-profit research institutions. However, TRDRP would have needed almost three times its budget to fund all research proposals that were evaluated as "outstanding" or "excellent" by expert peer reviewers. Looked at in another way, the program was able to fund only the top third of all scientifically worthy proposals. Details of 2006 awards, including abstracts, can be found in TRDRP's Compendium of Awards, which can be accessed at <http://www.trdrp.org/publications/compendiums/Comp06.pdf>.

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

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

- **Award Types**

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

or proven methods, it is creative, intellectually exciting, and shows clear promise to yield findings that could lead to breakthroughs in the field.

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

- **Cornelius Hopper Diversity Award Supplements**

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

Table 2. CHDAS awarded in 2006

<i>Trainee</i>	<i>Mentor</i>	<i>Institution</i>	<i>Grant title</i>
Marie Boman	Dr. Nada Kassem	San Diego State University Research Foundation	Water pipe use, SHS exposure & home policy in Arab Americans
Heather Mercer	Dr. Deborah Morton	University of California, San Diego	Diabetes & tobacco exposure in So CA American Indians
Malena Ramos	Dr. Bonnie Halpern-Felsher	University of California, San Francisco	Relationship of perceived risks and benefits to teen smoking
Romina Romero	Dr. George Matt	San Diego State University Research Foundation	Expos children to second hand smoke through contaminated homes

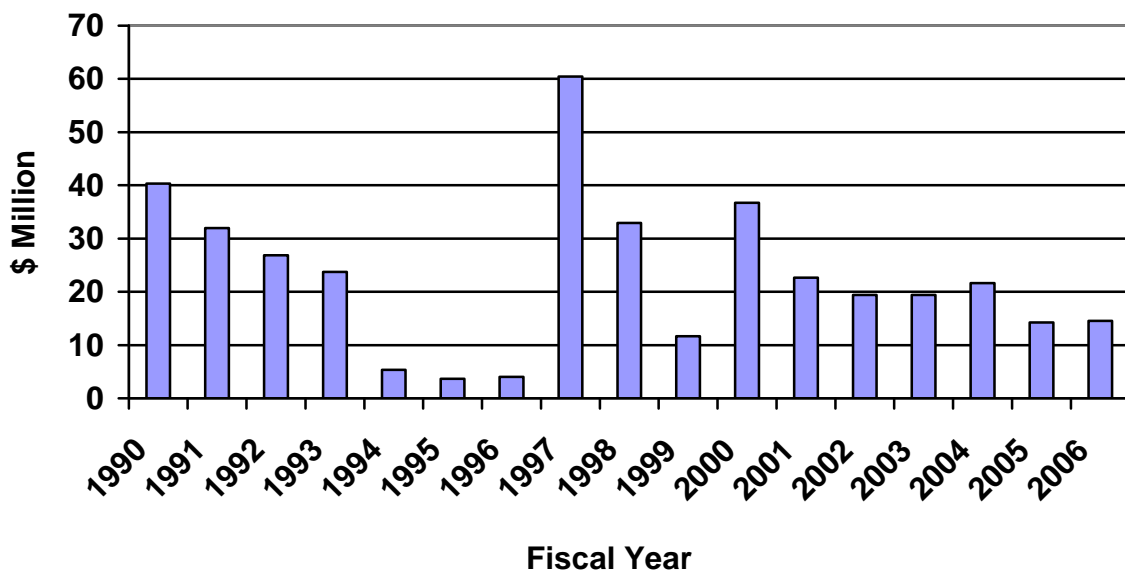
<i>Trainee</i>	<i>Mentor</i>	<i>Institution</i>	<i>Grant title</i>
Arnab Mukherjea	Dr. Lisa Bero	University of California, San Francisco	Corporate strategies: design, conduct, publication of research
Jane Pham	Dr. Lesley Butler	University of California, Davis	Tobacco, acculturation and gastric cancer among Hispanics
Nuong Hong	Dr. Jean Gehricke	University of California, Irvine	Nicotine & behavioral regulation in adult ADHD
Toby Howard	Dr. Cornelia Pechmann	University of California, Irvine	Use of entertainment education on TV to deter youth smoking
Brian Soller	Dr. Juliet Lee	Pacific Institute for Research and Evaluation	Environmental contexts of smoking for Southeast Asians
Kathy Akagha	Dr. Sora Tanjasiri	California State University, Fullerton	Environmental influences on tobacco use among AAPI communities

HISTORY

Appropriations

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

Figure 2: Appropriations to TRDRP from Proposition 99 Research Account, 1990-2006



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 more than \$5 million which is now 24 percent of the total available.

Grants Awarded

Since its inception in 1989 through 2006, TRDRP awarded \$373 million in 1,164 grants to approximately 800 scientists at 80 California institutions. The grants awarded constituted 24 percent of the applications received. The dollar amounts and number of grants awarded by subject area are displayed in Table 1.

Table 1. Award Totals by Subject Area, 1989-2006

<i>Subject Area</i>	<i>Number of Awards</i>	<i>Amount (\$)</i>
Cancer	225	\$61,136,702
Cardiovascular Disease	140	\$44,130,896
Epidemiology	149	\$58,341,303
General Biomedical Science	129	\$31,889,561
Nicotine Dependence	130	\$36,006,259
Public Health/Policy	119	\$32,464,173
Pulmonary Disease	141	\$39,571,964
Tobacco Control	131	\$55,302,324
Total	1,164	373,279,463

Evaluation of Research Grant Applications

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

SCIENTIFIC ADVISORY COMMITTEE

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

Table 3. Scientific Advisory Committee Roster, 2006

<i>CHAIR</i>	<i>REPRESENTING</i>	<i>TERM</i>
Fredric B. Kraemer, M.D. Professor of Medicine Division of Endocrinology Stanford University Medical Center Stanford, CA 94305-5103	American Heart Association, Western States Affiliate	2005-2008
<i>MEMBERS</i>		
Carlene E. Henriques, CHES Program Coordinator Sacramento County DHHS Tobacco Education Project 9719 Lincoln Village Drive, Suite 300A Sacramento, CA 95827	Community-based provider of health education and prevention services	2005-2008
Paul Murata, MD, MSPH Medical Institute of Little Company of Mary 20911 Earl Street, Suite 400 Torrance, CA 90503	American Cancer Society, California Division	2005-2008
Geraldine V. Padilla, Ph.D. Professor & Associate Dean for Research UCSF School of Nursing 2 Koret Way, Room N339 San Francisco, CA 94143-0604	Professional medical or health organization	2005-2008
Gerd P. Pfeifer, Ph.D. Professor of Biology Beckman Research Institute, City of Hope 1500 E. Duarte Road Duarte, CA 91010	Biomedical research	2004-2007
Kim D. Reynolds, Ph.D. Associate Professor Institute for Health Promotion & Disease Prevention Research Keck School of Medicine University of Southern California 1000 South Fremont Avenue, Unit 8 Alhambra, CA 91803	Independent research university	2005-2008

MEMBERS	REPRESENTING	TERM
Thomas Scott, Ph.D. Vice President for Research San Diego State University 5500 Campanile Drive San Diego, CA 92182	Tobacco-related disease research institution	2004-2007
Randall S. Stafford, M.D., Ph.D. Associate Professor of Medicine Stanford Prevention Research Center Stanford University Medical School Hoover pavilion, Room N229 211 Quarry Road Stanford California 94305-5705	Independent research university	2005-2008
Ken Yoneda, M.D. Associate Professor Division of Pulmonary and Critical Care Medicine University of California, Davis 4150 V Street, Suite 3400 Sacramento, CA 95817	American Lung Association of California	2003-2006

RESULTS OF COMPLETED RESEARCH GRANTS, 2006

This section summarizes research findings from grants that ended in 2006.

Nicotine Dependence

Smoking-Induced Dopamine Release: Bupropion Effects (11RT-0024)

Arthur L. Brody, M.D.

Brentwood Biomedical Research Institute

Previous research using PET scan images demonstrated that the chemical dopamine is released in the brains of humans when they smoke a cigarette. Reductions in craving for cigarettes were associated with the extent of dopamine released, indicating that dopamine release is associated with the rewarding properties of nicotine. This study investigated whether smoking-induced dopamine release is attenuated by a course of treatment with Zyban (bupropion HCl) an antidepressant medication known to help smokers quit.

Thirty-five smokers received Zyban and 35 placebo, while an additional 10 controls received a single PET scan. Initial analyses indicated that pre-treatment smoking resulted in dopamine release and Zyban (but not placebo) treatment normalized (increased) smoking-induced dopamine release. There was also an indication that greater smoking-induced craving reduction is associated with greater dopamine release.

Irritant and Analgesic Effects of Nicotine (11RT-0053)

Earl E. Carstens, Ph.D.

University of California, Davis

The investigators hypothesized that nicotine has two major sensory effects: (1) irritation upon contact with the oral and ocular mucosa or skin, which may contribute to the liking tobacco products (analogous to preference for spicy foods), and (2) analgesia due to activation of pain-inhibitory systems in the brain, which may contribute to dependence.

These studies showed that nicotine delivered to the throat or tongue similarly activated neurons in regions of the brain stem representing the face and mouth (i.e., the trigeminal subnucleus caudalis, or Vc) and the throat (i.e., nucleus of the solitary tract or NTS). Electrophysiological studies revealed that neurons in these brain stem regions are strongly excited by nicotine acting through neuronal nicotinic acetylcholine receptors expressed in pain receptors of the oral cavity. They also found interactive effects of nicotine, menthol (often added tobacco for its cooling action), and other irritants on neuronal responses to hot, cold and chemical stimuli. The significance of these findings is that pain and irritation can be evoked by nicotine (in second-hand smoke, smokeless tobacco, etc.) through specific nicotinic receptor mechanisms, and that activation of nicotinic receptors is also required to initiate cellular mechanisms leading to a reduction in pain, irritation and certain tastes. Human psychophysical studies showed that nicotine reduces the sensitivity of the tongue to subsequent nicotine-evoked irritation for more than 24 hr, and that nicotine reduces the perceived intensity of sweet and bitter tastes (but not salty, sour or savory), findings largely consistent with nicotine's centrally-mediated inhibitory effect on taste neurons in NTS. Nicotine also reduces palatability via reduction of sweetness, thereby reducing the palatability of food which leads to reduced consumption.

Analgesia (reduced pain sensitivity) in rats following exposure to cigarette smoke was prevented by mecamylamine (a nicotine receptor blocker) and naltrexone (an opiate receptor blocker), indicating that nicotine is critical to the pain-reducing effect of smoke exposure.

Nicotinic Receptors, Smoking and PD (11RT-0237)

Lorene M. 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. This was the first study to investigate the role of nicotinic receptors in this association. The brain contains several different types of receptors for nicotine, and some are found in the basal ganglia, the area of the brain affected by PD. Animal studies have shown that the nicotine from cigarette smoke stimulates nicotinic receptors, which in turn could interfere with the dopamine cell loss caused by environmental chemical exposure, or enhance the release of dopamine, the brain chemical that is deficient in PD.

The research found support for the hypothesis that if the protective effect of cigarette smoking is conferred by the action of nicotine on acetylcholinergic receptors in brain, the inverse association of cigarette smoking with PD would be largely restricted to subjects with functioning nicotinic receptors (i.e., those who carried wildtype rather than variant alleles for the nicotine receptor genes). For several of the nicotine receptor genes under study, the inverse association of

smoking with PD existed only if the subject carried two wildtype alleles, whereas the protective effect of smoking was not observed for subjects who carried one or two mutant (variant) alleles; this “gene-environment interaction” was statistically significant for several of the nicotinic receptor subunit genes under study.

Nicotine Self–Administration in an Animal Model (12RT-0099)

George F. Koob, Ph.D.

Scripps Research Institute

These neurobiological studies: (a) investigated the cause of a major component of the motivation to continue to smoking once dependent, (b) helped identify individual differences that may lead to vulnerability to dependence, and (c) identified key targets for future medications development for the treatment of nicotine dependence. Rats were found to self-administer nicotine to the point of dependence (addiction) and showed a striking increase in nicotine intake during certain periods of the daily cycle. Nicotine self-administration was altered by various nicotinic neuropharmacological agents. Rats given escalating doses of nicotine with intermittent 2-day abstinence periods took significantly more nicotine than rats given continuous access to the same unit dose of nicotine. When rats that were self-administering nicotine were exposed to social stress, they showed profound changes in food and water intake but no changes in nicotine intake.

The Effects of Nicotine Upon Brain Activity and Neurocognition in Schizophrenia (12KT-0176)

Kirsten Fleming, Ph.D.

University of California, Irvine

Approximately 90% of schizophrenics smoke compared with less than 25% of the general population in the US. This study tested the hypothesis that this very high rate is due to the fact that nicotine compensates for a defect in frontal lobe function and hypometabolism in schizophrenia. Neuronal circuitry involved in the effects of nicotine and of nicotine withdrawal was measured via PET scan, with all subjects scanned twice following overnight abstinence from nicotine. Comprehensive neurocognitive evaluations and mood ratings were also obtained.

Schizophrenics reacted dramatically to nicotine administration with overall bilateral activations, but there were no significant changes in brain activity for the normal controls. Further, and importantly, nicotine significantly enhanced memory in the schizophrenics. This improvement in memory function, was greater than the changes documented by novel antipsychotic medications which are touted as having cognitive enhancing properties. These findings suggest that schizophrenics may smoke in order to change their brain functioning and improve their memory. By elucidating the specific brain mechanisms involved in nicotine and schizophrenia, it is hoped that new treatments (likely nicotinic-related) may be developed to aid smoking cessation in schizophrenia.

Hyperactive Nicotinic Receptors (12RT-0245)

Henry A. Lester, Ph.D.

California Institute of Technology

Nicotine enhances the release of dopamine, a chemical neurotransmitter that induces a feeling of pleasure, which is a key factor in addiction. Knowing specifically which receptor molecules are activated by nicotine in the dopamine-releasing cells would be a promising first step in developing a therapeutic drug to help smokers break the stranglehold of addiction. This project

determined that when cell receptors with a specific subunit known as alpha4 are activated by nicotine, this is sufficient for some addiction-related events, such as reward behavior, sensitization, and tolerance. This finding suggests that alpha4, and the molecules that are triggered in turn by alpha4, may prove to be useful targets for addiction intervention therapies.

In work to identify nicotinic receptor subtypes that were sufficient to elicit nicotine dependence, the “partner” alpha4 subunit suspected in addiction was examined. But instead of experimenting with a knockout mouse, “hypersensitive knock-in” mice were developed. Investigators replaced a naturally occurring bit of DNA with a mutation that changed only a single amino acid in only one of the mouse’s 30,000 genes; but that change made the alpha4 subunit highly sensitive to nicotine. As hypothesized, the mice with the re-engineered alpha4 receptor proved to be highly sensitive even to very small doses of nicotine that did not activate other nicotinic receptor types. This finding shows the alpha4 subunit is a prime candidate to be studied at the molecular and cellular level, and as a possible target to develop a medication that would reduce the nicotine-induced release of dopamine, hopefully reducing nicotine’s addictive grip on smokers.

Nicotinic Receptors at GABAergic Synapses in the Hippocampus (13FT-0005)

Jingming Zhang, Ph.D.

University of California, San Diego

Nicotinic acetylcholine receptors (nAChRs) containing alpha7 gene product are the most abundant and highly expressed in hippocampal interneurons in the brain. Since the hippocampus is essential for the production of new declarative memories, nicotinic signaling in the hippocampus is an obvious target for understanding nicotine’s role in tobacco use. Alpha7-nAChRs were found to be highly expressed by interneurons in hippocampus and the receptors co-localize in part with GABA receptors, suggesting interactions may exist between the two types of receptor. Endogenous nicotinic signaling through alpha7-nAChRs appears to modulate GABAergic responses in the interneurons. Some intracellular protein kinases, including calcium/calmodulin dependent kinase (CaMK) and mitogen-activated protein kinase (MAPK), are involved in the mechanism of the modulation.

Cognitive Effects of Gestational Nicotine (13DT-0033)

Shahrdad Lotfipour, Ph.D.

University of California, Irvine

The investigators hypothesized that that nicotine may interact with other constituents in tobacco smoke to produce its addictive effects because nicotine alone is only weakly reinforcing in animals. One such constituent is known to be an irreversible monoamine oxidase inhibitor (MAOI). One-hour MAOI pretreatments with tranylcypromine, an irreversible MAO A and B inhibitor, can enhance nicotine self-administration, mediated through an increase in nicotine-induced dopamine release in the nucleus accumbens (an area of the brain associated with drug reward). However, measurements of neurotransmitter levels in the brain via *in vivo* microdialysis found that these pretreatments had pharmacological effects other than the inhibition of monoamine oxidase. When these non-specific effects were attenuated by extending the MAOI pretreatment time from 1 to 20 hours, nicotine reward was increased. Results also suggest that MAOIs may differentially influence nicotine self-administration in males and females.

Ethnic and Gender Variation in Nicotine Detoxification (12KT-0234)

Huijun Z Ring, Ph.D.

Scripps Research Institute

Glucuronidation plays a major role in the detoxification of nicotine and other tobacco toxins and is carried out by UDP-glucuronosyltransferase enzymes (UGTs). A reduction in the rate of nicotine glucuronidation may cause the accumulation of tobacco toxins in the body and lead to an elevated risk of tobacco-related cancer. The objectives of this project were to: 1) identify UGT gene variants in three different ethnic groups (European Americans, African Americans, and Asian Americans); 2) characterize study subjects for these DNA variants; and, 3) investigate the effect of these polymorphisms on *in vivo* nicotine detoxification phenotypes. The results indicate that genetic variation in the *UGT2B7* gene contributes to interindividual differences in nicotine glucuronidation. Gender and ethnic differences were observed in the effects of *UGT2B7* genetic variation on nicotine glucuronidation.

Nicotine Effects on Gene Expression and Metaplasticity (13FT-0059)

Damian Wheeler, B.Sc., Ph.D.

Stanford University

These experiments examined the mechanisms by which nicotinic acetylcholine receptors (nAChRs) signal to the nucleus, an essential step in the long-term neuronal adaptation that may underlie nicotine addiction. The results demonstrated that nicotine strongly activates a protein called CREB in the nuclei of sympathetic neurons. Much previous work has suggested that nAChRs cause calcium channels to open and the calcium channels then mediate the signal to CREB. This research found that the drugs used to block the calcium channels also blocked nAChR; therefore, it is not possible to use them to attribute a role for calcium channels. Further, these findings are important because calcium channel drugs are used therapeutically in heart disease and some of their effects may result from their action on nAChR.

Tobacco-Use Prevention and Cessation

Pager-Assisted Smoking Cessation Study (11RT-0009)

Timothy P. Carmody, Ph.D.

University of California, San Francisco

While prevalence of smoking in other age groups has declined, prevalence among persons 18 to 24 years rose from 23% in 1991 to 27% in 2000. This was a randomized controlled trial of the effectiveness of pager-transmitted therapeutic messages to help young adult smokers quit. Among 226 participants followed at 3 months, 30% in the pager-assisted group reported having quit, compared with 25% in the control group ($P=0.37$). Quit rates validated by saliva cotinine analyses were 19% in the pager-assisted group versus 12% in the control group at 3 months ($P=0.15$). Among 197 participants assessed at 12 months, the same percentage reported that they quit in the pager and control groups, 18%. Quit rates validated by saliva cotinine analyses were 14% in the pager-assisted group versus 11% in the control group ($P=0.67$). Therapeutic pager messages did not increase the success rate over standard counseling during the year of follow-up. Therapeutic pager messages combined with nicotine patches would appear to compare favorably with standard behavioral counseling and nicotine patches. As an alternative to pagers, mobile

cell phones could serve as a medium for sending smoking cessation text messages to adult smokers.

Internet Enhanced Proactive Telephone Counseling (11RT-0096)

Leslie A. Lenert, M.D., M.S.

Veterans Medical Research Foundation

This research studied how best to use the Internet to enhance the effects and decrease the costs of treatment methods that use counselor-initiated telephone calls timed to smokers' quit efforts. Of the 648 smokers asked about enrollment in the study, only 219 or one-third enrolled. The most common reason given for not enrolling was not having Internet access or not using the Internet to check e-mail frequently (418 of 648). Seventy enrollees received Internet-only follow-up care, 75 received both the Internet and telephone, and the remaining received telephone only. Though it is feasible to deliver part of the telephone counseling process by the Web and e-mail, less than half the smokers who had Internet access and e-mail set up an account on the Web site. In follow-up studies (67% of enrollees contacted), most smokers thought that the counseling should include some Web-based component.

Tobacco Prevention/Cessation in Continuation High Schools (11RT-0209H)

Steve Sussman, Ph.D.

University of Southern California

A classroom-based approach to teen smoking cessation can provide nearly 100% reach and retention of smokers and might provide a preventive effect on light smokers/nonsmokers. The main goal of this research was to improve teen cessation by adapting to a classroom setting in continuation high schools a TRDRP-funded, model school-based clinic cessation program that was taught only to high school smokers. Tobacco use was assessed through multiple measures (i.e., 30-day use, last 7 day use, tobacco involvement, and CO measurement).

The 8 classroom sessions were compared to classroom assessments only, with immediate pretests, immediate posttests, 6- and 12-month follow-up assessments, in a two-group experimental design. The intervention resulted in: (a) a larger increase in accurate answers to questions about program-specific items; (b) a lower weekly smoking rate, but not a lower monthly smoking rate or change on a tobacco involvement measure, which indicates the full range of nonsmoking to smoking; and (c) a cessation effect on weekly smoking at posttest and both follow-up time points. The aim to train school-based trainers for the classroom program was postponed.

Test of an Internet Virtual World for Teen Smoking Cessation (11HT-3301H)

Susan I. Woodruff, Ph.D.

San Diego State University Research Foundation

This participatory research study of a smoking cessation intervention for teens involving both academic and school partners used an Internet-based, virtual reality world combined with motivational interviewing conducted in real-time by a smoking cessation counselor. Real-time interaction between smokers and professional change agents and among smokers themselves might be the key variable in the success of such an approach to cessation. Teen smokers recruited from high schools in San Diego County participated in up to seven 45-minute virtual world sessions over a 7-week period, and completed online surveys at baseline, post-

intervention, 3-months and 12-months post-intervention. They were compared to adolescents who only completed online surveys. Fifty-four percent were male. Fifty-one percent were Hispanic, 28% White non-Hispanic, 5% African-American, 7% Asian/Pacific Islander, and 9% other ethnic groups. Forty-one percent were from continuation/alternative high schools and the others from regular high schools.

Participants were significantly more likely than controls to report at the immediate post-intervention assessment that they had abstained from smoking during the past week, smoked fewer days in the past week, smoked fewer cigarettes in the past week, and considered themselves a former smoker. However, positive effects were generally not maintained at long-term follow-up, suggesting that real-time Internet communication may be an effective approach to help young smokers quit or reduce smoking in the short-term, but that additional support (e.g., booster sessions) is probably needed for longer-term success.

A Web-Based Support Community as a Tool for ST Cessation (12IT-0169)

Margaret M. Walsh, Ed.D.

University of California, San Francisco

This pilot study assessed the feasibility and acceptability of using an interactive Web site to promote cessation of smokeless tobacco (ST) use by male college baseball athletes. The Web site included virtual chat rooms to provide “real time” interaction with cessation counselors and other ST users, and a professionally-monitored message board. Six California colleges were randomly assigned to either an interactive Web site group or a usual care control group. ST users in the experimental group were referred by their athletic trainers to the Web site for help with stopping ST use.

One month post baseline, ST users were reassessed on patterns and correlates of ST use by a mailed questionnaire and a structured telephone interview. The electronic message board provided access to seek support and ask questions about quitting. The message board and Web pages, which contained information on preparing to quit and managing the initial quit period, and the interactive elements were deemed acceptable and feasible to implement. Based on these pilot results, the investigators plan to seek funding to further develop and test the Web site with 26 California colleges. There were many difficulties maintaining a large enough base of ST users to sustain a chat room experience, even when it was scheduled so it was eliminated.

Tobacco Control Policy

Tobacco Use and Policies: San Diego Mexican American Residents (11RT-0148H)

Melbourne F. Hovell, Ph.D., MPH

San Diego State University Research Foundation

This project estimated the prevalence and identified the determinants of smoke-free home policies, exposure to environmental tobacco smoke (ETS), smoking, and cessation among residents of Mexican descent, emphasizing the influence of acculturation, social factors, and demographic and contextual variables. It also tested the hypothesis that increased exposure to community-wide anti-tobacco programs, such as the California Tobacco Control Program, is associated with lower rates of smoking and ETS exposure, higher rates of home policies banning

smoking, and significant differences regarding theoretical determinants of tobacco-related behaviors.

Respondents in San Diego (N=1,103), Tijuana (N=400), and Guadalajara (N=400) were surveyed on rules regarding smoking in the home, tobacco use, ETS exposure, and history of tobacco-related diseases, as well as a broad range of theoretical determinants of tobacco use, exposure, and policies. Results revealed the influence of individual and environmental variables on tobacco-related behaviors of Mexican-descent populations. The results supported the hypothesis of a positive association between the level of exposure to the California Tobacco Control Program and differences on smoking, smoking policies, ETS exposure, and theoretical determinants. Results from this study will inform theory and practical public health interventions for tobacco control targeting Mexican Americans in Mexico and the U.S. and set the stage for international cooperation for tobacco control.

Modeling Cost/Effectiveness of Tobacco Control Programs (11RT-0243A)

Robert M. Kaplan, Ph.D.

University of California, Los Angeles

A mathematical model is being developed to estimate the public health effects of tobacco use. Health status in populations can be represented by two concepts. First, the model must take into consideration how long people live and how much the average life expectancy is reduced as a function of tobacco use. The second component is quality of life. In traditional survival analysis, a person is scored as 1.0 if they are alive and 0.0 if they are dead. Our model values level of health on a continuum between optimal health and death. If, a person lives a year with a tobacco related illness that makes quality of life half as good as optimal, the model assigns one half year of credit. Various levels of wellness are valued so that survival time can be quality adjusted. Over the last year the model has been refined and can now estimate the impact of tobacco use using data from the National Health Interview Survey. The model shows that those who begin smoking as teenagers lose about 3.5 quality adjusted years of life between ages 18 and 70 in comparison to those who never smoked. About one third of the quality adjusted years life list is attributable to shortened life expectancy and two thirds is attributable to reduced quality of life. During the final phase, the project will estimate the impact of various tobacco control policies using the model.

Use of Existing Data to Develop New Tobacco Control Strategies (12RT-0082)

Karen Messer, Ph.D.

University of California, San Diego

This research used existing data from population surveys of tobacco use attitudes and behavior to evaluate existing tobacco control policy and inform future tobacco control policy. Broad strategies for evaluation are: (1) to compare trends in California with those in the rest of the U.S., including among diverse subpopulations; (2) to investigate school-based and other tobacco control efforts which target adolescents; and (3) to examine the effects of prices and smoking restrictions on tobacco use attitudes and behaviors in California. Research to inform future policy includes study of the adolescent smoking uptake process, including influences such as tobacco industry advertising and promotions, study of young adult smoking behavior, and of adult cessation patterns.

The research documented a dramatic decline in per capita cigarette consumption in California, about 30% of which can be directly attributed to reduced smoking initiation. Adolescents who came of age during the California Tobacco Control Program had much lower overall rates of smoking uptake than previous cohorts, although importantly this was *not* true for those with known risk factors for smoking. Using longitudinal data, the ongoing effectiveness of tobacco industry advertising and promotions among receptive adolescents was documented, as well as increases in tobacco industry promotional activity. Other important findings include that California's comprehensive Tobacco Control Program has increased smoking cessation among young adults, compared with states which used cigarette excise taxes alone to discourage smoking, or states with less well funded tobacco control programs. This occurred against a background of rising cessation rates among smokers of all ages in the U.S. The comprehensive California program is also shown to have reduced consumption levels among continuing smokers of middle age, who have the lowest cessation rates. Prevalence of smoking among non-Hispanic white adults declined significantly faster in California in the 1990's and did not decline significantly in comparison states. However, among African Americans during this period there was a nationwide reduction in smoking prevalence attributed to reduced smoking uptake among younger African American cohorts.

Geography of Underage Tobacco Retail Sales in Los Angeles (12RT-0093)

Robert I. Lipton, MPH, Ph.D.

Pacific Institute for Research and Evaluation

The overall rate of underage tobacco sales in Los Angeles increased from 34.1% in 2001 to 39.1% in 2003. Zip codes that had considerably higher rates, 60-100%, had much lower mean family income, much higher percentage of foreign-born residents, and greater population density. Areas of denser and poorer population are more likely to have schools close to tobacco outlets, a greater proportion of which sell to minors. More than 56% of all violations occurred within 1,000 feet of a school. These results, particularly school and tobacco outlet distance information, were used by the Los Angeles City Attorney's Office to support new city legislation requiring tobacco vendors to register with the city and pay a yearly fee.

California AB 13 Compliance and Ethnicity in Urban Bars (12RT-0116)

Roland S. Moore, Ph.D.

Pacific Institute for Research and Evaluation

This ethnographic study was designed to gain a qualitative understanding of how and why urban stand-alone bars serving patrons from different ethnic groups in Los Angeles and San Francisco counties either comply or fail to comply with California Assembly Bill 13 (AB 13), a workplace smoking ban that in 1998 was applied to bars statewide. The study used semi-structured interviews and highly structured and qualitative observations. Smoking was much more likely in bars serving Asian patrons than those serving Irish or Latinos. This finding was different from a previous study in which Irish and Asian bars were not complying. Indoor smoking was much more likely when only one bartender was present, when a bartender was smoking, and when ashtrays were available. Qualitative data from the interviews with enforcement officials representing public health, fire, and law enforcement charged with enforcing AB 13 revealed institutional and legal barriers to easily enforcing the law in some bars. Interviews with patrons, bartenders, and owner-managers of bars revealed that female bartenders who were low socioeconomic status were more likely to be exposed to secondhand smoke.

Smoking Cessation and Medical Care Use/Costs in a Large HMO (12RT-0216)

Hai-Yen Sung, Ph.D.

University of California, San Francisco

This study analyzed the impact of smoking cessation on the utilization and costs of medical care services for members in a large HMO in California. Receiving a physician's advice to quit smoking in the last 12 months significantly increased the likelihood of a quit attempt by both men (OR=1.46) and women (OR=1.64). Furthermore, female smokers who both participated in the smoking cessation programs and used nicotine replacement drugs in the past 12 months were more likely to quit (OR=1.61). Other than this finding, participation in smoking cessation programs and use of nicotine replacement drugs did not have significant effects on successful quitting.

Compared to never smokers, the per person excess costs for current smokers were \$413 for females and \$1,171 for males. The excess costs for former smokers increased immediately after quitting and peaked during the first 5 years. After quitting five years, the excess costs for former smokers were generally lower than those for current smokers except for females. By gender, the excess costs were \$787 versus \$413 for females, and \$754 versus \$1,171 for males. By age, the excess costs were \$49 versus \$88 for the younger age group, \$611 versus \$1,042 for the middle age group, and \$1,255 versus \$1,514 for the older age group.

Tobacco Use among American Indian Adolescents in California (12RT-0253H)

Jennifer B. Unger, Ph.D.

University of Southern California

American Indian (AI) adolescents have a higher prevalence of tobacco use than any other ethnic group in California. This study used existing statewide datasets and collected new focus group data to obtain information about tobacco-related attitudes and behaviors among AI adolescents in California, including their tobacco use patterns, their psychosocial and cultural risk and protective factors, and their reactions to tobacco control efforts. A Cornelius Hopper Diversity Award Supplement to this grant added a survey of AI community leaders about the use of traditional tobacco in their communities.

Several themes emerged from the focus groups, including the adolescents' introduction to tobacco at early ages, their current easy access to tobacco from social and retail sources, their views on traditional vs. commercial tobacco use, their perceptions of commercial tobacco advertisements that use AI imagery, and their widespread exposure to secondhand smoke at home, at AI events, and at casinos. The results of the quantitative analyses were consistent with the focus groups in identifying easy access to tobacco, smoking friends and family members, and lack of home smoking bans as risk factors for smoking. The interviews of adult AI community leaders echoed these themes and identified several others, including regional variation in access to homegrown tobacco, gender variation in roles in traditional rituals involving tobacco, and attitudes toward Native-owned cigarette brands. These findings will inform the creation of more culturally appropriate tobacco prevention programs for AI youth in California.

Disproportionate Cost of Smoking for Communities of Color (13RT-0030)

Wendy Max, Ph.D.

University of California, San Francisco

Estimates of the economic burden of smoking for California's African American and Hispanic populations will provide policymakers and leaders in these communities with a better basis for developing programs and policies that will mitigate the impact of smoking. This study, which is developing models of smoking-attributable costs for African Americans, Hispanics, and others in California, has three specific aims: (1) to estimate the direct health care costs of smoking-related illness; (2) to estimate the value of lost productivity from smoking-related illness; and (3) to estimate the losses resulting from smoking-caused mortality. It is also considering intangible costs imposed on the African American community in terms of the loss of grandparent caregivers. Preliminary results suggest that for African Americans, Hispanics, and others, smoking currently or in the past predicts an increased probability of smoking-related disease (SRD). For all three groups, older people are more likely to have had a SRD. African Americans and others with a high school education were less likely to have had a SRD. Those most likely to report being in poor health in all three groups were daily smokers (compared to nonsmokers) and older people. More educated people were less likely to report poor health. Hispanic heavy drinkers were more likely to report poor health than other Hispanics. Hospital expenditures were highest for African Americans with education beyond high school and with Medicaid or private insurance. Ambulatory care expenditures were higher for those in all three groups who were older, educated, had health insurance, and African Americans who were severely overweight.

Among smokers, African American grandparent caregivers were more likely to have a smoking-related disease than African American parents and non-African American parents and this was particularly true for cardiovascular disease. African American grandparent caregivers who smoke had higher annual per person health expenditures than those who did not smoke (\$6,714 vs. \$4,406). Even among smokers, African American grandparent caregivers had higher health expenditures (\$6,714) than all other parents (\$2,895), African American parents (\$2,662), and non-African American parents (\$2,490). This result was true for expenditures on home health care, hospital care, professional services, and drugs.

Secondhand Smoke Contamination and Resale Value of Cars (13IT-0042)

Georg E. Matt, Ph.D.

San Diego State University Research Foundation

Nonsmokers are exposed to very high doses of secondhand smoke (SHS) when smoking takes place in a car with closed windows and the ventilation turned off. New research indicates that the chemicals in SHS can accumulate in dust and attach to a car's interior surfaces and emit SHS for months even if no further smoking takes place. Controlled laboratory studies and this investigator's study of smokers' homes suggest that some materials used in cars may be particularly good SHS reservoirs (e.g., upholstery, carpeting, and ceiling liners).

This study was the first to explore whether smoking leads to residual SHS pollution of cars and affects its resale value. Air, dust, and surfaces were examined in a random sample of 129 used passenger cars for sale by private parties in the San Diego metropolitan area.

Detectable levels of residual SHS pollution were found in all smokers' cars. Compared to nonsmokers' cars, nicotine concentrations in smokers' cars were 4-7 times greater (dust), 10-24 times greater (surfaces), and 5-24 times greater (air). When smokers prohibited smoking in their cars, the nicotine contamination levels were 47% lower (dust), 58% lower (surfaces) and 79% lower (air) than in cars without smoking restrictions. However, even when smokers' prohibited smoking in their cars, nicotine levels were 4-10 times higher than in nonsmokers' cars. Smokers' cars lost 9% of their value compared to nonsmokers' cars, controlling for age, make, and value.

Lesbian, Gay, Bisexual and Transgender Tobacco Use (13RT-0084)

Elisabeth P. Gruskin, DrPH

Kaiser Foundation Research Institute

Though most research on lesbians, gays, and bisexuals (LGBs) indicate that these groups have higher smoking rates than the general population, most studies have used convenience samples or analyzed datasets with a small number of LGBs. Research has yet to identify the factors to contribute to LGB tobacco use or exposure to secondhand smoke. The present study found that LGBs have an elevated rate of cigarette smoking. In the first statewide random sample of LGB households in California, the study found that 28.7% of Lesbians (95% confidence interval [CI]=21.2%, 38.0%), 26.9% of Bisexual women (95% CI=19.5, 35.9), and 43.6% of women who have sex with women (WSW) (95% CI=35.9, 51.5) were current smokers compared to 12.1% of women in general (95% CI=11.9, 12.4). Current smoking was higher when also comparing Gay men (27.3%, 95% CI=21.6, 33.8) to men in general (19.7%, 95% CI=19.2, 20.3). LGBs had lower rates of cigar and smokeless tobacco use.

Supply and Demand for Tobacco Dependence Coverage (13RT-0141)

Helen A. Halpin, Ph.D.

University of California, Berkeley

This research estimated the current supply and demand for employer-sponsored health insurance coverage for effective tobacco dependence treatments (TDTs: including nicotine replacement therapy [NRT], Zyban, and behavioral therapy). With nearly 21 million Californians enrolled in private health insurance plans, increasing coverage for effective smoking cessation treatments has the potential to reduce significantly the number of smokers in the state and the adverse health consequences and health care costs attributable to smoking. The current availability of coverage for smoking cessation treatments was determined by analyzing the 2005 Kaiser/HRET California Health Benefits Survey of a random sample of 1,339 firms that offer their employees health insurance benefits.

Forty-five percent of firms in California cover any TDT. The percentage of firms covering Zyban increased significantly since 2000 from 15% to 23%. The largest firms significantly increased coverage for Zyban, NRT, and comprehensive TDT benefits. The percentage of workers covered in 2005 for any TDT (62%), NRT (54%), Zyban (44%) and comprehensive TDT benefits (29%) also increased significantly since 2000. For workers enrolled in HMOs, coverage rates of Zyban have increased significantly. For workers enrolled in PPOs, coverage of all TDTs increased significantly.

The current demand for employer-sponsored health insurance coverage for smoking cessation treatments was determined by analyzing population data from the 2003 Next Generation

California Tobacco Control Alliance survey of a random sample of 608 insured adult Californians. Sixty percent of respondents agreed that health insurers should be required to cover TDTs as part of their standard benefits and 52% of respondents would be willing to pay higher premiums to finance such coverage. Those most likely to support a benefit mandate for TDTs were current smokers (70%) and those who believed smoking is an addiction (64%) and that treatments are effective (70%). Those least willing to pay a higher premium to finance coverage for TDTs include men, those with annual household incomes below \$25,000, never smokers, and those who identify themselves as politically conservative.

Persons enrolled in Blue Shield of California's Individual and Family PPO plans were randomly assigned to one of three treatment groups: (1) coverage for Free and Clear's proactive telephone counseling and pharmacotherapy conditional on enrollment in the counseling program; (2) coverage of pharmacotherapy (unconditionally) and the Free and Clear telephone counseling; or (3) coverage for pharmacotherapy only. No differences were found in sustained quit rates as a function of benefit design, but significantly higher rates of quit attempts and quit rates for 7 or more days over the study period were found for those who used the benefits compared to those who did not. The only factor predicting 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.

Cancer

Smoking, Microsatellite Instability and Gastric Cancers (10RT-0251)

Anna H. Wu, Ph.D.

University of Southern California

In a recent study of sporadic colon cancer, cigarette smoking significantly increased the risk of microsatellite instability (MSI), a type of genetic change that is believed to promote cancer development by accelerating the accumulation of mutations. Another type of genetic change that is commonly found in colon and gastric cancer patients with MSI tumors is DNA methylation of the MLH1 gene. DNA methylation is a type of chemical modification of DNA that can be inherited without changing the DNA sequence. In addition, there are suggestive data that DNA methylation levels are higher among current smokers with lung cancer than never smokers with lung cancer.

This goal of this population-based cross-sectional study was to determine the frequency of MSI-high, MSI-low, and MSI-stable gastric cancers in a sample of 719 patients. Among gastric cancer patients with adequate DNA materials, 8 of 283 (2.8%) were classified as MSI-high and 10 (3.5%) were classified as MSI-low. DNA methylation of the MLH-1 gene was determined on 194 gastric cancer patients but only one patient was determined to be positive for MLH-1 DNA methylation; this person was also classified as MSI-high. The very low prevalence of MSI-H and MSI-L tumors in this cross-sectional study was unexpected. Because of the low prevalence, we were not able to investigate meaningfully the main question of interest for this study, namely, whether cigarette smoking increases the risk of MSI-H gastric cancers or DNA methylation of the MLH-1 gene. Contrary to our hypothesis, our results, in fact, suggest a small deficit of

current smokers among gastric cancer patients classified to have MSI-H/MSI-L tumors. However, given the very small numbers, this is very likely a chance finding.

p53 and p14ARF: Multiple Pathways of Lung Cancer Suppression (11RT-0074)

Ruth A. Gjerset, Ph.D.

Sidney Kimmel Cancer Center

The p53 and p14ARF tumor suppressors are cellular proteins that work together to trigger a cellular “self-destruct” mechanism (apoptosis) that prevents the proliferation of abnormal cells and thereby provides one of the first lines of defense against cancer. Unfortunately, most if not all malignant lung cancer cells lose either p53 function or p14ARF function and are thus devoid of this important barrier to tumor cell growth. This study investigated a novel biological strategy for lung cancer treatment that exploits these two tumor suppressors, and elucidated the less-well understood p53-independent tumor suppressor activity of p14ARF.

The study found that: (1) The p53/p14ARF gene combination was extremely potent at triggering tumor cell death through apoptosis and could therefore provide a highly effective, non-toxic biological therapy for lung cancer that exceeds the efficacy of current gene transfer vectors. (2) A macrophage-mediated bystander effect was triggered by tumor cell apoptosis. (3) Topoisomerase I, an essential cellular enzyme and important chemotherapeutic target, is a p14ARF binding protein in lung cancer cells. Adenoviral-mediated transfer of p14ARF can enhance the sensitivity of lung cancer cells to camptothecin, a finding that has important implications for lung cancer treatment, particularly for patients who have acquired resistance to camptothecin. By providing a basis for an improved, non-toxic, biological approach to lung cancer treatment and identifying a role for p14ARF in the tumor cell response to conventional therapy, this study could have a major impact on treatment success for a broad array of lung cancers that fail conventional therapy.

Molecular Predictors of Oral Cancer Development (11RT-0141)

Richard C. Jordan, DDS., Ph.D.

University of California, San Francisco

Although an important risk factor for oral cancer is the presence of epithelial dysplasia, most lesions will not progress to malignancy and there are few reliable markers of those that will progress to oral cancer. The goal was to validate specific biomarkers as potential predictors of oral cancer development. A list of potential biomarkers was identified by screening oral cancer specimens using expression microarrays (“gene chips”). Then, the feasibility of using the a number of biomarkers was examined using real-time quantitative PCR applied to RNA extracted from paraffin embedded tissue biopsies. Several promising molecular biomarkers that may predict the development of oral cancer were identified, while others did not differentiate between dysplasias that progress from those that do not: (1) Cathepsin L was significantly overexpressed in oral dysplasias that progressed to oral cancer compared to those that were not. (2) MMP-1 and MMP-9 proved to be significant predictors of oral cancer development in patients with oral dysplasias. (3) Many markers that appear to be overexpressed at the mRNA using expression microarrays are not when validated by real time PCR (i.e., VCAM, MgSOD, MMP2). (4) Some markers that are overexpressed in oral cancers and dysplasias do not differentiate dysplasias that progress from those that do not (i.e., CuSOD, EGFR, VEGF).

Involvement of the PI3K Pathway in Bladder Cancer Invasion (11KT-0236)

Colleen A. Sweeney, Ph.D.

University of California, Davis

Most bladder cancers (~ 80%) present as superficial disease, confined to the bladder mucosa or lamina propria with no muscle invasion. While superficial bladder tumors are amenable to bladder-sparing therapy, at least half of these tumors will recur. Among those that recur, 10-20% will progress to muscle invasive disease. Existing therapies for muscle-invasive disease still result in nearly 50% mortality and patients suffer a poor prognosis. An in-depth understanding of the molecular mechanisms underlying bladder cancer invasion should facilitate the development of more reliable treatment strategies.

A common theme in tumor progression is the aberrant activation of cellular signaling pathways. This study focuses on the role of the PI3K/Akt signaling pathway in mediating bladder cancer invasion. The study found: (1) A survey of 93 human bladder tumors found that 43% displayed aberrant activation of the PI3K/Akt pathway, indicating that this pathway could contribute to the growth and progression of a significant number of bladder tumors. (2) Inhibition of the PI3K/Akt pathway in bladder cancer cells by pharmacological agents or by expression of the pathway antagonists PTEN or dominant negative Akt drastically inhibited invasion, indicating that activation of this pathway is necessary for bladder cancer invasion. (3) Examination of human bladder tumors for aberrant activation of downstream targets of the PI3K/Akt pathway and found that the S6 ribosomal protein is highly phosphorylated in approximately 35% of tumors. Of note, this arm of the pathway is efficiently inhibited by the FDA-approved drug rapamycin, an analogue of which is already in clinical trial for several forms of cancer. We found that treatment of bladder cancer cells with rapamycin sensitized those cells to conventional chemotherapy, suggesting that rapamycin or its analogues could be combined with such therapies to improve patient response. Of most significance, we found that rapamycin inhibited the invasion of highly invasive bladder cancer cells. Since rapamycin is well tolerated clinically, these findings suggest that rapamycin or its analogues could be utilized in the treatment of invasive bladder carcinoma.

Novel DNA Vaccines for the Treatment of Lung Cancer (12RT-0002)

Ralph Reisfeld, Ph.D.

Scripps Research Institute

This research developed and critically evaluated novel DNA-based vaccines against lung cancer in mouse tumor models. The tumor's blood supply was drastically suppressed with a vaccine against a growth factor overexpressed on proliferating cells in the tumor microenvironment. A small molecule of nine amino acids was identified as the target of the vaccine to provide a more flexible and economically more favorable alternative to vaccination with a large and complex protein molecule. In addition, considerable progress was made in overcoming multiple drug resistance that seriously hinders the treatment of lung cancer by identifying an alternative vaccine approach that could overcome this stricture. A truly novel vaccine against lung cancer was developed by targeting a molecule called survivin which specifically prevents the effective killing of lung cancer cells. By inhibiting the action of survivin with a specific vaccine, lung tumor cells as well as other cells that are crucial in supplying such tumor cells with blood essential for their nourishment and growth could be killed more effectively. This double action vaccine proved most effective in eradicating lung cancer that had spread and established itself in

other organs in the body, thereby markedly increasing the life-span of the experimental animals suffering from lung cancer and in some cases even prevented the recurrence of this disease.

The research developed a novel and highly effective strategy to kill lung cancer cells by not only attacking them but also the very microenvironment in which they live and grow. The vaccine administered together with cyclophosphamide, a drug often used for cancer chemotherapy, were far more effective in killing lung tumor cells and preventing their spread than either alone. The research proved that a small molecule called inducible nitric acid was primarily responsible for this particular improvement in lung cancer therapy.

Targeting Hypoxia-Inducible Factor to Treat Lung Cancer (12KT-0111)

Siva Kumar Kolluri, Ph.D.

Burnham Institute of Medical Research

Hypoxia, a shortage of oxygen reaching tissues the body, plays a crucial role in tumor progression. The effects of tumor hypoxia are mediated by Hypoxia-inducible factor 1 (Hif-1), a transcription factor. Agents that inhibit Hif-1 signaling have therapeutic potential for inhibiting cancer progression. This research identified small molecule inhibitors that disrupted Hif-1 transcriptional activity by two different approaches. First, a homology model of Hif-1 alpha was generated to screen synthetic compound databases containing 750,000 compounds. Virtual ligand screening resulted in identification of 33 putative binders of Hif-1. Three of these compounds inhibited hypoxia-induced gene expression in cancer cells. Second, screening of chemical libraries employing cell-based systems resulted in the identification of five additional inhibitors of Hif-1. The investigators identified a novel cross-talk between nuclear receptor and Hif-1 signaling that can be exploited to develop novel Hif-1 inhibitors and are now evaluating the effect of Hif-1 transcriptional inhibitors on Hif-1 biological function in several cancer cell lines.

Integrins and Drug Resistance in Small Cell Lung Cancer (12RT-0143)

Kristiina Vuori, M.D., Ph.D.

Burnham Institute of Medical Research

Small cell lung cancer is a smoking-related disease with a poor prognosis. Most patients initially respond to chemotherapy, but almost invariably relapse and become resistant to chemotherapeutic treatment. Therefore, the patient 2-year survival rate remains less than 5%. Most chemotherapy drugs are thought to work by activating self-destruction mechanisms in cancer cells known as apoptosis. Previous work by these investigators and others demonstrated that certain molecules that are on the cell surface, known as integrins, can block suicide signals against various stimuli in normal cells. This project yielded several novel insights into the mechanisms of drug resistance in lung cancer and outlined a path forward how to leverage these basic molecular-level findings to early-stage drug discovery efforts.

The study found support for the hypothesis that integrins, when overactivated, could be crucial for the development of drug resistance by blocking chemotherapeutic agent-induced death in cancer cells. Thus, ligation of certain integrins protects cancer cells against chemotherapeutic drug-induced suicide. Importantly, this protective effect was diminished by inhibitory anti-integrin antibodies in cell culture models. The findings also advanced understanding of the mechanisms by which integrins instruct the cancer cells not to commit suicide. Specifically, an

intracellular molecule named PI 3-kinase was identified as a crucial mediator of survival signaling downstream of integrins. Integrins appear to activate the PI 3-kinase pathway by activating the tyrosine kinase activity of the epidermal growth factor receptor (EGFR) in cancer cells. Very importantly, integrins activate the EGFR in a qualitatively different manner than its cognate ligand, EGF, does, which is especially important in light of ongoing clinical trials in lung cancer with EGFR inhibitors.

The Role of hCDC4 Regulation of Cyclin E in Lung Cancer (12KT-0151)

Charles H. Spruck, Ph.D.

Sidney Kimmel Cancer Center

This research project explored the role of a protein called hCdc4/Fbxw7 in lung cancer. hCdc4/Fbxw7 was hypothesized to belong to a class of proteins called tumor suppressors that act as “brakes” for cell division and halt tumor formation in humans. This research yielded several important findings including: (1) Identifying hCdc4/Fbxw7 as a tumor suppressor in lung tumorigenesis, associated preferentially with small cell lung cancer. (2) Mapping of a part of the hCdc4/Fbxw7 protein that localizes it to the nucleus for recognition of substrates. (3) Discovering an association between hCdc4/Fbxw7 and the chromosome segregation process. (4) Finding that hCdc4/Fbxw7 regulates the DNA damage response through the tumor suppressor protein p53.

Chemotherapeutic Inhibition of Polysialic Acid Biosynthesis (12RT-0254H)

Jacquelyn Gervay-Hague, Ph.D.

University of California, Davis

Certain cell surface proteins operate normally during embryonic development by acting as anti-adhesive factors that loosen the connections between cells thus allowing developing cells to move, often over long distances. One of these, $\alpha(2,8)$ -Linked polysialic acid (polySia), performs this vital task by covalently bonding to neural cell adhesion molecules called N-CAMs, thus loosening the connections between the cells. In several human cancers, polySia becomes inappropriately expressed and becomes a factor that favors tumor cell detachment and spread, i.e., metastasis. Metastasized cancers are notoriously difficult to treat and therapeutics that inhibit this process are highly sought after. During embryonic development as well as during carcinogenesis, PolySia is synthesized from a carbohydrate called CMP-Sialic acid by specific enzymes called polysialyltransferases. This project was devoted to the synthesis and biological evaluation of neutral analogs of CMP-Sialic acid that would be capable of neutralizing polysialyltransferases by binding to them, turning off the inappropriate production of polySia in cancer patients, and thus inhibiting metastasis.

The work led to the development of analogues that were effectively taken up by cancer cells *in vitro* and that successfully inhibited very specific polysialyltransferases. These new findings provide a powerful platform on which to design anti-metastatic chemotherapeutics to treat cancer patients based on their specific tumor characteristics, i.e., which polysialyltransferases they express. Keeping tumors localized can make cancer much easier to treat, anti-cancer therapies more successful, and permanent remission a more likely therapeutic outcome.

Genomics and Transcriptome of Oral Precancer Progression in Smokers (13KT-0028)

Xiaofeng C. Zhou, Ph.D.

University of California, Los Angeles

The goal of this project was to identify a set of candidate genes that have high functional relevance to oral squamous cell carcinoma development and a molecular-based prediction model for oral precancer progression. The investigators optimized a set of genomic technologies to perform genome-wide profiling on oral precancer samples. They then performed the genomic analysis on a set of paired progressive and non-progressive oral precancer samples and demonstrated the frequent allelic imbalance at 8p and 11 q22 in oral precancer lesion. They developed several statistical and bioinformatics tools for the concurrent analysis of diversified genomic data sets. The strategic combination of these aspects will eventually lead to the generation of genetic based diagnostic tool for the early detection of oral pre-cancer lesions with potential to transform into cancer.

Note.- This project was terminated one year early because the principal investigator moved to a university in another state.

Ephb4-Mediated Inhibition of Cell Death in Head and Neck Cancer Cells (14DT-0125)

Ram Kumar Subramanyan, M.D.

University of Southern California

For their survival, cells rely on signals from proteins called receptors that form channels of communication between the external milieu and the cells' internal environment. Cancer cells often overexpress different kinds of receptors thereby gaining a survival advantage. The investigators have shown that EphB4 is one such cell surface protein that is frequently overexpressed in head and neck cancers and provides survival signal to the cancer cells. Biological therapy that targets EphB4 holds promise as a new paradigm for treating head and neck cancers.

The research showed that EphB4 protects cancer cells from a potent cancer-specific body defense mechanism that is mediated by a protein known as TRAIL. Whereas normal cells are not affected by TRAIL, cancer cells are particularly sensitive to TRAIL-induced cell death. Overexpression of EphB4 confers to cancer cells resistance to TRAIL and provides them a growth advantage. Depleting TRAIL-resistant cells of EphB4 renders them sensitive to TRAIL. Conversely, forced expression of EphB4 in TRAIL-sensitive cells abolishes their sensitivity to TRAIL. We have also shown that the portion of the protein EphB4 that protrudes outside the cell is sufficient to overcome TRAIL-induced cell death, a unique function, hitherto unknown. Therapeutic compounds that target EphB4 are under development with the aim that knocking down EphB4 in human cancers will restore their sensitivity to the body's own cancer fighting mechanisms, such as TRAIL.

Heart and Lung Disease

LDL Pathophysiology and Lipoprotein Structure (12RT-0014)

Robert O. Ryan, Ph.D.

Children's Hospital Oakland Research Institute

Vascular damage that occurs as a result of tobacco smoke exposure is related, in part, to altered metabolism of plasma lipoproteins. When damaged by smoke-related oxidation events, low-density lipoproteins (LDL or “bad” cholesterol) are no longer recognized by the LDL receptor. The plasma protein, apolipoprotein E (apoE), can function as a ligand for (i.e., bind to) members of the LDL receptor family. This research is focused on the role of apoE as a determinant of lipoprotein metabolism. Results obtained provide insight into the structural dynamics of apoE and the relationship between the existence of protein conformational sub-populations and atherogenic potential. The anticipated effect of this process on lowering plasma LDL levels will be of benefit to individuals who are susceptible to oxidative damage to LDL as a result of tobacco smoke exposure.

The results indicate that a mutation at one end of the apoE3-NT four-helix bundle markedly enhances the lipid binding activity of this protein. Experiments assessing the role of a specialized structural motif present in apoE, termed a leucine zipper, found that it confers stability to the apoE3-NT helix bundle state and may serve to modulate lipid binding activity of this domain and, thereby, influence the conformational transition associated with manifestation of LDLR binding activity. Likewise, in lipoprotein binding assays, mutant apoE3-NT protected human LDL from phospholipase C induced aggregation to a greater extent than wild-type apoE3-NT.

Smoking-Related Changes in LDL and Atherosclerosis (12KT-0104)

Yury Miller, M.D., Ph.D.

University of California, San Diego

Cigarette smoke induces oxidative modifications of low-density lipoprotein (LDL), the particles that carry cholesterol. Macrophages, professional “scavenger” cells in atherosclerotic lesions, accumulate large quantities of oxidized LDL (OxLDL) and become so-called foam cells, with large intracellular lipid deposits. Accumulation of OxLDL and foam cells in the artery wall initiates development of atherosclerosis, the disease underlying heart attack and stroke. It now becomes clear that atherosclerosis is an inflammatory disease, in which macrophage foam cells are the major pro-inflammatory cells.

The investigators recently discovered that minimally modified (oxidized) LDL (mmLDL) binds to a cell surface receptor CD14 and activates another receptor TLR4. The function of these two receptors is to detect microbial invasion and to give the cell a signal to mobilize its anti-microbial defenses. CD14/TLR4 senses the presence of various forms of bacterial lipopolysaccharide (LPS). These novel data provide an interesting link between immune responses to bacterial infection and to oxidation-specific components of self, such as mmLDL.

The investigators found that, in addition to the cell surface CD14, soluble CD14 in plasma also bound mmLDL, thereby mediating mmLDL interactions with TLR4 on many cell types. Cigarette smoke oxidized LDL is minimally oxidized but it differs from biologically generated mmLDL in the pattern of cell signaling it induces in macrophages. Using macrophages from

TLR4 knockout mice, different classes of mmLDL effects were characterized, which are dependent or independent of TLR4. Differences in the activation of signaling pathways and gene expression by mmLDL and by LPS were characterized. These signaling differences provide a background for synergistic effects of mmLDL/LPS in inducing inflammation and, possibly, promoting atherogenesis.

Antiatherogenic Helical Segments of ApoA-1 (13IT-0025)

John K. Bielicki, Ph.D.

Lawrence Berkeley National Laboratory

Short-term exposure to cigarette smoke has a negative impact on the cardiovascular system, including plasma lipids and lipoproteins. Smokers have low levels of high-density lipoprotein (“good” cholesterol or HDL) cholesterol, which is a major risk factor for development of cardiovascular diseases, such as atherosclerosis. HDL can protect against cholesterol accumulation in the artery wall, related to its major function in stimulating cholesterol efflux from macrophage foam-cells in plaque lesions. This process of cholesterol efflux produces HDL and involves a critical interaction between a membrane transporter known as ABCA1 and helical apolipoproteins such as A-I and E. The nature of this interaction is not known, but such knowledge could lead to the development of small molecules that promote aortic cholesterol egress and reductions in plaque lipid accumulation.

These studies revealed that the C-terminal domains of apoA-I and E were responsible for activity in mediating ABCA1-dependent cholesterol efflux. Moreover, it was discovered that negatively charged amino acids were important for conferring ABCA1 activity. The information was translated into a small peptide with potent and selective properties in mediating cholesterol efflux via ABCA1. The peptide is roughly 50- to 100-fold more potent than existing mimetic peptides in stimulating cholesterol efflux, which represents a major breakthrough in the field. Therefore, this research succeeded in isolating the essential determinants of apoA-I and E responsible for the ABCA1 interaction and created a highly potent peptide that has many experimental and clinical uses.

Regulation of Epithelial Cell Polarity and Lung Disease (13FT-0159)

Minji Kim, Ph.D.

University of California, San Francisco

The lung is a branching tree of tubes, with the final branches ending in tiny air sacs. The tubes and air sacs are lined by a single layer of cells called epithelial cells which form a crucial barrier between the air we breathe and the interior of the organism. The epithelial cells are directly exposed to the harmful and carcinogenic chemicals in tobacco smoke. Damage to the epithelial cells leads to at least two major types of tobacco-related disease. First, most lung cancers arise from epithelial cells. A hallmark of lung cancer is that the cells lose their polarity. Indeed, the degree of loss of polarity correlates with the severity of the disease. Second, Chronic Obstructive Pulmonary Disease (COPD) involves changes to the architecture of the lung, including epithelial polarity. The onset of malignancy is normally associated with the loss of polarity and organized tissue structure. Understanding the regulatory factors involved in epithelial tissue morphogenesis is therefore essential for understanding the development of COPD.

Cell polarity is controlled in most cell types by a master regulator, a complex of proteins known as Par3, Par6, atypical Protein Kinase C (aPKC) and Cdc42. Epithelial cells were grown in three-dimensional gels and studies were conducted of how the Par6 complex regulates polarity and tissue structure in epithelial cysts. The studies found that GFP-Par6 is enriched at the apical region of cyst, which is consistent with the localization of aPKC. Overexpressions of Par6 mutants did not induce the inversion of polarity by immunofluorescence analysis. However, the N-terminal deletion of Par6 (DNPar6), which prevents its interaction with aPKC, causes a significant increase in cell death during cyst formation. Consistently, cleaved caspase-3, a marker of cell death, is activated in DNPar6 cells. Furthermore, aPKC and GSK-3b, a substrate of aPKC, participate in regulating cell death/proliferation in epithelial cell cyst formation. These results suggest that the Par6/aPKC complex may not only regulate cell polarity but could be important for cell death. This observation will provide new insights into the pathogenesis and progression of lung cancer and may help in discovering new therapeutics, diagnostics, and prophylaxis.

Oxygen Radicals in Biology GRC 2006 (14ST-0191)

Henry J. Forman, Ph.D.

University of California, Merced

The conference was held in Ventura, California on February 5-10, 2006 and was co-chaired by Henry Jay Forman, Ph.D. University of California, Merced, and Rafael Radi, M.D., Ph.D., Universidad de la República, Montevideo, Uruguay. The Conference Co-Vice Chairs were Stanley L. Hazen, M.D., Ph.D., Lerner Institute, Cleveland Clinic, and Kevin Moore, MB.BS., Ph.D., FRCP, University College, London

TRDRP funding was used to cover the travel expenses of junior faculty, postdoctoral fellows and graduate students from California institutions.

Sunday night: The chemistry of redox signaling led by Garry Buettner (University of Iowa) with presentations by Jon Fukuto (UCLA) and Aron B. Fisher (University of Pennsylvania).

Monday morning: Iron homeostasis and nitric oxide metabolism and emerging technologies and biomarkers in free radical biology led by Balaraman Kalyanaraman (Medical College of Wisconsin) with presentations by Jean Claude Drapier (Centre National de la Recherche Scientifique, Gifonsuron Yvette, France), David M. Krzywanski (University of Alabama at Birmingham), Ronald Mason (National Institutes of Health, USA), Ohara Augusto (Instituto de Química- Universidade de São Paulo, Brazil), and Silvina Bartesaghi (Universidad de la República, Montevideo, Uruguay).

Monday evening: NADPH oxidases in signaling led by John Eaton (University of Louisville) with presentations by David Lambeth (Emory University) and Tom Leto (National Institutes of Health, USA).

Tuesday morning: Oxidants-antioxidants in infection and inflammation led by Etsuo Niki (Human Stress Signal Research Center, Midorigaoka, Ikeda, Japan) with presentations by Madia Trujillo (Universidad de la República, Montevideo, Uruguay), Horacio Botti (Universidad de la

República, Montevideo, Uruguay), Paolo Di Mascio (Universidade de São Paulo, Brazil), Stefan Rytter (University of Pittsburgh), and Alireza Mani (University College London).

Tuesday evening: Lipid derived radicals and nitric oxide led by Rafael Radi with presentations by Homero Rubbo (Universidad de la República, Montevideo, Uruguay) and Paul Baker (UAB).

Wednesday morning: Thiol oxidation in signaling led by Robert Floyd (Oklahoma Medical Research Foundation) with presentations by Matilde Maiorino (University of Padova, Italy), Alessandra Rinna (University of California, Merced), Tak Yee Aw (Louisiana State University), P Boon Chock (National Institutes of Health, USA), and Fernando Antunes (Instituto de Investigação Científica Bento da Rocha Cabral, Lisboa, Portugal).

Wednesday evening: Business meeting followed by a session on sources of reactive species led by Kelvin Davies (University of Southern California) with presentations by Edgar Pick (Sackler School of Medicine, Tel Aviv University, Israel) and Paul Brookes (University of Rochester).

Thursday morning: Redox and electrophilic signaling led by Lester Packer (University of Southern California) with presentations by Masayuki Yamamoto (University of Tsukuba, Japan), Douglas Thomas (National Institutes of Health, USA), Michel Toledano (Service de Biologie Moléculaire Systémique, Gif-sur-Yvette, France), and Aimee Landar (UAB).

As this conference occurred on the 25th anniversary of the first Gordon Conference on Oxygen Radicals in Biology, a panel discussion on “What Have We Learned In Twenty Five Years Of Oxygen Radical Gordon Conferences And What Do We Still Need To Learn?” was led by Henry Jay Forman (the Conference Co-Chair) and involved Kelvin Davies, Balaraman Kalyanaraman, John Eaton, Etsuo Niki, Robert Floyd, Garry Buettner, Norman Krinsky, and Lester Packer, who were all present at the first conference and are still active in the field.

On Thursday evening, Christine Winterbourn (New Zealand) delivered the Conference Plenary Lecture, “Understanding oxidative stress: From the chemistry of superoxide to the lungs of babies.” The session was chaired by Norman Krinsky (Tufts University).

2006 American Lung Association of California Annual Conference (14ST-0192)

Lynn Devine

American Lung Association of California

The 2006 American Lung Association of California Annual Conference, co-sponsored by TRDRP was held in San Diego, California on October 19 - 21. A longtime ALAC volunteer, Christine Bryant, helped start the conference by focusing on the mission and vision of the American Lung Association of California. There were sessions on lung cancer, COPD, Proposition 86, and global warming. Approximately 100 scientists attended, including postgraduate and graduate students, and research administrators. One major sub-theme of the conference was the nationwide Performance Based Management System (PBMS), which is a basic tool for planning the objectives and the measurement of successes. The PBMS is flexible and powerful system to help increase work efficiency that integrates state and national organizations with excellent connectivity and delivery of services at the community level.

Oxygen Club of California (14ST-0193)

John J. Maguire, D.D.S.

Oxygen Club

The Oxygen Club of California annual meeting on Oxidants and Antioxidants in Biology, co-sponsored by the Linus Pauling Institute, was held in Santa Barbara on March 15-18, 2006, at Fess Parker's Doubletree resort. More than 200 people attended, with participation by leading academic and industry scientists. Keynote Lectures were delivered by Professors Arne Holmgren and Sten Orrenius, from Stockholm, Sweden. In addition, an exceptional cadre of internationally acclaimed scientists presented 33 talks on different aspects of obesity and metabolic syndrome, oxidative stress and uncoupling proteins, micronutrient action, dietary modulation of cell signaling pathways mitochondrial function on aging and disease and, other topics. The relationship between oxidative stress and tobacco smoke induced oxidative damage in biology is well established. Presentations by Jairam et al., on acrolein induced oxidative stress, Levy et al., on nSMase2 activation by tobacco smoke, and Webber et al., on mild CO exposure and oxidative stress are all research presentations on tobacco smoke and oxidative damage. The poster sessions included about 80 presentations and were on display throughout the meeting. The posters provided a forum for active and lively scientific exchanges. A grant from the California Tobacco-Related Disease Research Program was specifically geared towards allowing California students and post doctoral fellows to attend this meeting. California students from UC Berkeley, UC Davis, UC Merced, USC, and Childrens Hospital Oakland Research Institute attended this meeting due to partial funding from this grant. Of note, an especially gifted student researcher from CHORI who was a high school senior, attended his first scientific meeting.

Environmental Tobacco Smoke and Effects of Tobacco Use on Reproductive Processes

Tobacco Alteration of TGF β 3 Control of Palatogenesis (11RT-0064)

Charles F. Shuler, DMD, Ph.D.

University of Southern California

Maternal smoking has been linked to an increased risk for the incidence of orofacial clefts in fetuses. One of the tobacco constituents to which fetuses are exposed *in utero* that might be directly responsible for cleft palate is N'-Nitrosornicotine (NNN). This research examined the effect of NNN on palatal fusion *in vitro* in palatal shelves that were dissected from Swiss-Webster mice at embryonic (E) day 13.5, and maintained in organ culture treated with or without NNN (0.01, 0.1, 1, 10 and 100 mM, respectively). The research found that NNN resulted in continued cell proliferation and marked reduction of cell death of the medial edge epithelium. The mechanism of action of NNN was linked to the MAP kinase family and distinct changes in protein phosphorylation were observed following NNN exposure. It was shown that NNN must bind to the receptor to cause the effect. The use of specific inhibitors of the receptor binding can be shown to eliminate the effect of NNN. The binding of NNN to the receptor results in the subsequent activation of the MAP kinase pathway. This MAP activation does not occur when

the binding to the nicotinic receptor is inhibited. Inhibition of palatal fusion does not occur when the MAP kinase pathway is specifically inhibited following NNN binding to the receptor. The results of these studies have shown that NNN has a direct effect on the palatal tissues and inhibits palatal fusion by altering the programs of differentiation of the cells. The ability to eliminate the effects of NNN using specific chemical inhibitors suggest that chemoprevention strategies could be developed to alter the craniofacial phenotypes resulting from exposure of the tissues to tobacco constituents.

Effect of Maternal Smoking on Early Human Development (12RT-0059)

Susan J. Fisher, Ph.D.

University of California, San Francisco

Our group has been testing the theory that the ill-effects of smoking and/or exposure to second-hand smoke on a woman's ability to become pregnant, stay pregnant and deliver a healthy baby are attributable, at least in part, to the damage that nicotine exposure does either directly to the baby or indirectly to the placenta. This transient organ physically attaches the baby to the mother, the first crucial step in pregnancy. In addition, the placenta is the sole source of nourishment for the baby during pregnancy. Thus, any activity, such as smoking, or exposure to a drug, such as nicotine, that compromises the baby or placenta could have serious negative consequences on pregnancy outcome, with permanent life-long damage another possibility.

With regard to placental cells, the investigators found that nicotine exposure downregulated expression of molecules that we know are required, during the early stage of development, to physically connect the baby to the uterus. Thus, the results of these experiments could explain why many smoking women are infertile or unable to maintain pregnancy beyond a few days or weeks. With regard to embryonic stem cells, they found that nicotine exposure caused several different kinds of damage. The negative effects included a decrease in the cells' ability to make copies of themselves, an important property that is required for normal growth. In some cases the cells died, which could also impair growth. They observed many of these same changes in placental tissues obtained from pregnant women who were exposed to smoke.

Birth Defects, Smoking and Host Susceptibility (12RT-0098)

Suzan Carmichael, Ph.D.

March of Dimes, California Birth Defects Monitoring Program

This research examined whether women who smoke are at increased risk of delivering infants with craniosynostosis (i.e., premature fusion of bones in the skull, which leads to skull and craniofacial deformities) or hypospadias (i.e., the urethral opening occurs on the underside side of the penis), and whether factors such as intake of multivitamin/mineral supplements modify this association. Though smoking during the first month of pregnancy was not associated with risk of craniosynostosis, smoking later in pregnancy was associated with increased risk, but only among mothers who smoked at least 15 or more cigarettes/day. That is, during the second trimester, the odds ratio for smoking < 5 cigarettes/day was 1.0 (95% CI 0.6, 1.8), but the odds ratio for smoking 15 or more cigarettes/day was 1.6 (0.9, 2.8), after adjustment for maternal age, education, race-ethnicity, sub-fertility, parity, folic acid supplement intake, body mass index, and study center. Among this subgroup of women, intake of vitamin supplements was protective against the negative effects of this level of smoking. Among women who did not smoke, adjusted odds ratios suggested that secondhand smoke exposure during pregnancy at home, but

not at work/school, was associated with moderately increased risk; the odds ratio for home exposure was 1.3 (95% CI 0.9, 1.9). Results followed a similar pattern for some, but not all, specific suture types, but numbers for some groupings were small. In conclusion, the results suggest moderately increased risk of craniosynostosis among mothers who were the heaviest smokers and who continued to smoke during pregnancy, and among non-smoking mothers who were exposed to secondhand smoke at home. The analysis of hypospadias did not provide evidence for an increased risk among women who smoke.

Maternal interview data from a completed case-control study that was conducted in California only were combined with newly generated genetic data derived from archived DNA specimens, to examine whether variant genotypes for several candidate genes are associated with risk of limb defects. Increased risk was observed for variants in several genes related to vascular development and function (NOS3, F5, TNF, and NPPA) and to the detoxification of cigarette smoke (NATI). Some support was found for the hypothesis that the effects of variant genotypes in the presence of maternal smoking, or in the absence of supplement intake, may exceed effects of any of these factors alone. The results suggest involvement of genetic variation of biologically relevant candidate genes, and gene-environment interaction, for some limb anomalies whose pathogenesis may be related to altered vascular tone or integrity.

Chronic CO Exposure Impairs the Developing Auditory System (13FT-0150)

Douglas S. Webber, Ph.D.

University of California, Los Angeles

These studies examined children's susceptibility to chronic exposure to secondhand cigarette smoke, and how these environmental insults cause oxidative stress and decrease auditory function. Mild chronic exposure to secondhand smoke can cause cellular deficits in the auditory system and in sensitive regions of the brain. Newborn infants whose mothers smoke are less readily aroused by auditory stimuli than infants whose mothers do not smoke, suggesting potential auditory deficits caused by smoke. This study is the first to demonstrate that inhaled carbon monoxide (CO) at chronic mild concentrations is linked to oxidative stress.

The research found interplay between iron availability and the impact of chronic CO exposure on the integrity of neurons in the spiral ganglia of the cochlea during development. The hypothesis is that when mild iron deficiency conditions exist in the intracellular environment, neurons of the spiral ganglion are protected from the adverse effects of chronic mild CO exposure. CO can inhibit the activity of the auditory system by reducing energy and disrupting the integrity of the cochlea by increasing hydroxyl-based free radicals by the Fenton reaction, and that some of these effects can be circumvented by reducing the availability of iron. The Fenton reaction is a chemical process in which iron and hydrogen peroxide are combined to produce hydroxyl radicals, creating oxidative stress in the inner ear in our experimental paradigm. Chronic CO exposure would be expected to produce a chronic condition of oxidative stress. An additional hypothesis was that prolonged exposure to very low levels of CO negatively impact critical enzymes of the electron transport chain, and increase the expression of neuronal nitric oxide synthase (nNOS). This increase in nNOS also increases the amount of nitrotyrosine occurring in the caudate-putamen region of the brain of animals chronically exposed to CO. Neuronal NOS is thought to increase from hypoxia. However, reducing the iron status with the addition of CO exposure does not increase the nNOS observed in the caudate-putamen region similar to CO

exposure alone. The importance of iron status indicates that simple hypoxia is not the entire answer. Though local hypoxia might contribute to the condition, CO appears to be causing more than hypoxia. In the iron adequate condition, the chronic mild CO exposure establishes a cellular environment unfavorable for normal cell development and function, by perturbing the dynamics of the appropriate signal processes for the normal course of neuronal development.