TRDRP
Tobacco-Related Disease Research Program

Tobacco-Related Disease Research Program
6th Annual Investigator Meeting
AIM 2001
Racial and Ethnic Disparities in Tobacco-Related Disease Research

STAFF

Susanne Hildebrand-Zanki, Ph.D.
Director

Francisco Buchting Ph.D.
Research Administrator,
Epidemiology and Policy Research

Phillip Gardiner, Dr.P.H.
Research Administrator,
Social & Behavioral Sciences/
Nicotine Dependence

Margaret Shield, Ph.D.
Research Administrator,
Biomedical Sciences

M.F. Bowen, Ph.D.
Program Evaluator

Editha Briones
Administrative Assistant

Carlin Colbert
Administrative Assistant

Sharon L. Davis
Media Designer

Lionel O. Greene, Jr., Ph.D
Scientific Analyst,
Biomedical Sciences

Teresa E. Johnson
Administrative Coordinator

Carolyn Robinson
Administrative Assistant

Christine Tasto
Scientific Analyst,
Behavioral/Policy/Epidemiology

AIM 2001

The Westin Hotel
Los Angeles Airport
5400 West Century Blvd.
Los Angeles, CA 90045
(310) 216-5858

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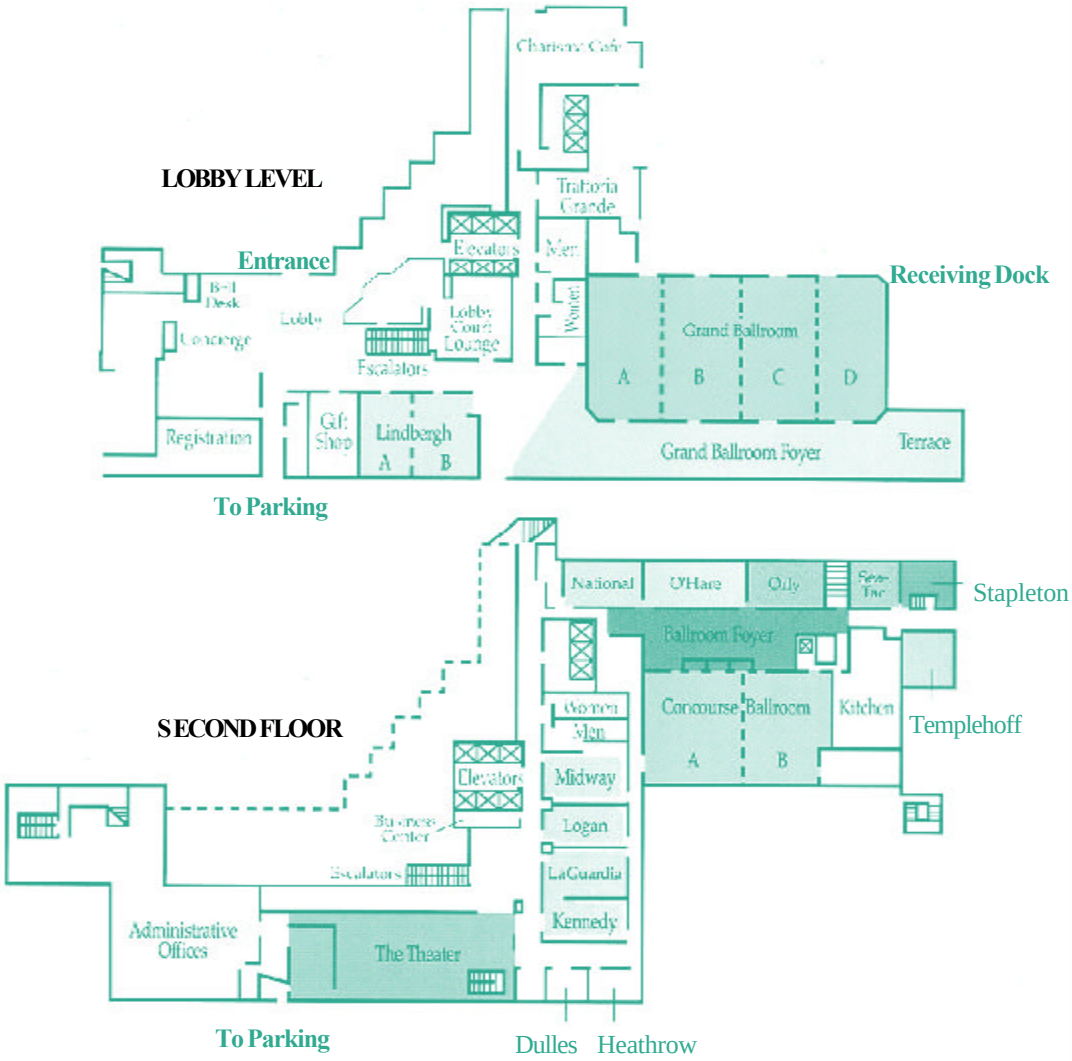
On behalf of the Tobacco-Related Disease Research Program staff and the University of California, I would like to extend a warm welcome to you to TRDRP's 6th Annual Investigator Meeting. Our theme for the plenary session is Racial and Ethnic Disparities in Tobacco-Related Research. The topic is of particular interest in California, which is one of the most diverse places in the world. This provides challenges to researchers and practitioners on many levels, from tobacco use prevention to treatment of disease. It also provides opportunities to include members from these diverse communities in research to advance our knowledge of their tobacco use patterns and susceptibility to tobacco-related diseases.

As always, I would like to encourage you to visit the poster sessions, especially those outside your own area of expertise to see what advances are being made in other fields to combat the detrimental effects of tobacco use.

I hope that this meeting will highlight the advances made in tobacco research, that it will provide ample opportunity for you to network with other investigators, and that it will stimulate discussions about emerging research questions and how we will collectively tackle them.

Susanne Hildebrand-Zanki



WESTIN - FLOOR PLAN

December 6th, THURSDAY

8:00 AM - END OF DAY - 2ND FLOOR LOBBY

REGISTRATION

(*Posters can be set up after 5:00 pm)*

9:30 AM -12:30 PM - ORLY

CARA/SARA Investigator Workshop

1:00 PM -5:00 PM - STAPLETON

(30 min. loop - every half hour)
Film: The Media and Tobacco Control

1:00 PM -5:00 PM - LA GUARDIA

Exhibits

1:30 PM - 4:30 PM
CONCURRENT WORKSHOP SESSIONS

KENNEDY

Racial/Ethnic Classification of Research Subjects
American Cancer Society - California Division, Inc.

MIDWAY

Advances in Atherosclerosis Research II
American Heart Association - Western States Affiliate

NATIONAL

Lung Cancer Research Highlights
California Thoracic Society/American Lung Association of California

LOGAN

The Secrets to Searching the Tobacco Industry Documents
Tobacco Control Archives - UCSF

O'HARE

Tobacco Control in Diverse Populations
Department of Health Services - Tobacco Control Section

5:00 PM - 6:30 PM - CONCOURSE BALLROOM A

TOWN HALL MEETING - Tobbacco Industry Funding of Research

6:30 PM - 7:30 PM - GRAND BALLROOM D

RECEPTION

DECEMBER 7th, FRIDAY

7:00 AM - END OF DAY - 1ST FLOOR LOBBY

REGISTRATION

7:30 AM - 9:30 AM

CONTINENTAL BREAKFAST & POSTER SET UP

9:00 AM - 12 NOON - GRAND BALLROOM A&B

PLENARY SESSION

Race, Ethnicity, Socioeconomic Status and Health
David Williams, Ph.D. - University of Michigan

Impact of Cultural Competence on Treatment Outcomes
Nolan Zane, Ph.D. - University of California, Davis

Biology as a Determinant of Health
Anna Wu, Ph.D. - University of Southern California

The Federal Perspective on Research Needs
Raynard Kington, M.D., Ph.D. - National Institutes of Health

12 NOON - 1:30 PM - GRAND BALLROOM C&D

LUNCHEON

1:00 PM -3:30 PM - STAPLETON

(30 min. loop - every half hour)
Film: The Media and Tobacco Control

8:00 AM -3:30 PM - LA GUARDIA

EXHIBITS

1:30 pm - 3:30 pm - POSTER SESSIONS

1:30 - 2:30 pm
- **A)** Epidemiology - ***Midway***
- **B)** Nicotine Dependence - ***National***
- **C)** ETS Measurement - ***Kennedy***
- **D)** Cancer Therapies & Screening - ***Kennedy***
- **E)** Reproductive Effects - ***Kennedy***

2:30 - 3:30 pm
- **F)** Policy & Economics - ***O'Hare***
- **G)** California Multicultural Communities - ***Orly***
- **H)** Cardiovascular & Pulmonary Diseases - ***Logan***

TOBACCO-RELATED DISEASE RESEARCH PROGRAM

CARA/SARA Investigator Workshop

Moderators

Francisco Buchting, Ph.D.
Research Administrator, Epidemiology and Policy Research

Phillip Gardiner, Dr. P.H.
Research Administrator, Social & Behavioral Sciences/Nicotine Dependence

9:30	***Welcome, review of agenda, the reiteration of the goals and logistical concerns***
9:40	***Conceptual Overview of Participatory Research***
9:55	***Introductions***
10:15	***Impact of Collaborative Research on the community and academic partners and the joint relationship***
11:05	***Break***
11:20	***Describe the genesis of the collaboration; what TRDRP award mechanisms were involved?***
11:45	***Identify strengths and weakness of the CARA/SARA award mechanisms***
12:10 pm	***Future Directions and Roundtable***

AMERICAN CANCER SOCIETY – CALIFORNIA DIVISION

Racial/Ethnic Classifications of Research Subjects

Moderator
John Simmons, M.D.
Senior Physician & Medical Oncologist
Kaiser Permanente Medical Center, Walnut Creek

1:30 – 2:00 ***Underrepresented Populations in Clinical Trials***
Georgia Sadler, Ph.D.
Associate Professor, University of California, San Diego

2:00 – 2:30 ***General Issues of Population Classification***
Lihua Liu, Ph.D.
Demographer, The Los Angeles County Cancer Surveillance Program

2:30 – 2:40 ***Break***

2:40 – 3:10 ***Classification Issues in the California Asian Population.***
Stephen McPhee, M.D.
Professor, University of California, San Francisco (invited)

3:10 – 3:40 ***Classification Issues in the California Hispanic Population.***
Lourdes Baezconde-Garbanati, Ph.D.
Assistant Professor, University of Southern California

3:40 – 4:30 ***Roundtable Discussion***

AMERICAN HEART ASSOCIATION – WESTERN STATES AFFILIATE

Advances in Atherosclerosis Research II

Moderator

Fredric B. Kraemer, M.D.

President, American Heart Association, Western States Affiliate
Professor, Stanford University School of Medicine

1:30 – 1:40 ***Welcome***
Fredric B. Kraemer, M.D.

1:40 – 2:15 ***The Role of Hormone Replacement Therapy in the Prevention of Atherosclerosis***
Howard N. Hodis, M.D.
Associate Professor of Medicine and Preventive Medicine
Director, Atherosclerosis Research Unit - University of Southern California

2:15 – 2:50 ***Atherosclerosis, Chylomicron Remnants, and Cigarette Smoke: Is There a Connection?***
Alen D. Cooper, M.D.
Professor of Medicine, Stanford University School of Medicine
Director, Palo Alto Medical Foundation Research Institute

2:50 – 3:00 ***Break***

3:00 – 3:35 ***Oxidative Stress and Atherosclerosis***
Alan M. Fogelman, M.D.
Professor and Executive Chair, Department of Medicine
UCLA School of Medicine

3:35 – 4:10 ***Reversible Hypercholesterolemia in a New Mouse Model***
Stephen G. Young, M.D.
Professor of Medicine, UCSF

4:10 – 4:30 ***Discussion***

CALIFORNIA THORACIC SOCIETY
AMERICAN LUNG ASSOCIATION OF CALIFORNIA

Lung Cancer Research Highlights

Moderator
Steven Dubinett, M.D.
Professor of Medicine, University of California, Los Angeles
Director, UCLA Lung Cancer Research Program

1:30 – 1:50 ***Putting the Problem of Lung Cancer in Perspective and a Review of What's to Come***
Steven Dubinett, M.D.
Professor of Medicine, University of California, Los Angeles

1:50 – 2:10 ***Role of Smad Protein in Growth Inhibition of Tumor Cells***
Kunxin Luo, Ph.D.
Staff Scientist, Lawrence Berkeley National Laboratory

2:10 – 2:30 ***Novel DNA Vaccines for the Treatment of Lung Cancer***
Ralph Reisfeld, Ph.D.
Professor of Medicine, The Scripps Research Institute

2:30 – 2:50 ***Chemopreventive Strategies Against Lung Cancer Recurrence.***
Jenny Mao, M.D.
Assistant Professor of Medicine, University of California, Los Angeles

2:50 – 3:00 ***Break***

3:00 – 3:20 ***Novel Regulatory Mechanisms for Lung Cancer Growth***
Randolph Hastings, M.D., Ph.D.
Associate Professor of Anesthesia, University of California, San Diego
Staff Physician, VA San Diego Healthcare System

3:20 – 3:40 ***Mobilized Dendritic Cells for Lung Cancer***
Edgar Engleman, M.D.
Professor of Pathology and Medicine, Stanford University School of Medicine

3:40 – 4:30 ***Roundtable Discussion***

CALIFORNIA DEPARTMENT OF HEALTH SERVICES TOBACCO CONTROL SECTION

Tobacco Control in Diverse Populations

Moderator
Jon Lloyd, M.A.
Chief, Data Analysis and Evaluation
California Department of Health Services, Tobacco Control Section

1:30 – 1:50 ***Differences in Tobacco-Related Behavior and Attitudes by Race, Ethnicity and Gender in the United States and California: A Comparative Analysis***
Jessica Shumacher, M.S., Research Scientist
Kristi Koumjian, M.S., Research Scientist
California Department of Health Services, Tobacco Control Section

1:50 – 2:10 ***Ethnic Differences in Correlates of Smoking Uptake and Youths' Exposure to Tobacco Control Programs***
Luanne Rohrbach, Ph.D., Assistant Professor
Jennifer Unger, Ph.D., Assistant Professor
University of Southern California

2:10 – 2:30 ***Disparities and advantages: A two-sided story of Hispanic tobacco use in California***
Hao Tang, Ph.D.
Research Scientist, California Department of Health Services
Tobacco Control Section

2:30 – 2:50 ***African American Smoking Behavior Results from the 1999 California Tobacco Survey***
Elizabeth A. Gilpin, M.S.
Cancer Prevention and Control Program
University of California, San Diego, Cancer Center

2:50 – 3:00 ***Break***

3:00 – 3:20 ***Smoking Cessation among Asian-Americans and Pacific Islanders***
Shu-Hong Zhu, Ph.D.
Associate Professor, University of California, San Diego

3:20 – 3:40 ***Standardization and Disparate Populations***
David Cowling, Ph.D.
Research Scientist, California Department of Health Services, Tobacco Control Section

3:40 – 4:30 ***Roundtable Discussion***

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
TOBACCO CONTROL ARCHIVES

The Secrets to Searching the Tobacco Industry Documents

Learn to search secret tobacco industry documents! Librarians and researchers from the UCSF Center for Tobacco Control Research and Education/Library for Knowledge Management provide hands-on experience, tips and tricks to help you mine this important resource for tobacco control and public policy. We will give examples of how tobacco industry documents have been used in tobacco control policy research.

Celia White, MLS
Director of Content And Services
Legacy Tobacco Document Library
University of California, San Francisco

Lisa Bero, Ph.D.
Professor, Dept. of Clinical Pharmacy/Inst. for Health Policy Study
University of California, San Francisco

1:30 PM - 4:30 PM

TOWN HALL MEETING: TOBACCO INDUSTRY FUNDING OF RESEARCH

Moderator

Dr. Kathy Sanders-Phillips
TRDRP Scientific Advisory Committee Member

Featured Participants

Dr. Tom Glynn
Director, Cancer Science and Trends, American Cancer Society

Dr. Scott Leischow
Chief, Tobacco Control Research Branch, National Cancer Institute

Dr. Susanne Hildebrand-Zanki
Director, Tobacco-Related Disease Research Program

Tobacco companies have provided millions of dollars to researchers in the United States and have also conducted their own internal research programs. This fact has been brought to the attention of the scientific research community again recently with the launch of the Philip Morris External Research Program and with the organization of a "Tobacco Science and Health Policy" conference sponsored by Brown & Williamson. With these programs, tobacco companies are encouraging researchers to join them in the efforts to make a "safer" cigarette.

What has been the impact of tobacco industry funding of research on the research community and on the public's perception of smoking risks?

Is it ever appropriate for researchers interested in promoting public health to accept funding from an industry whose products are inherently unhealthy?

Can the positives of tobacco-industry funding of research justify the negatives?

If researchers refuse tobacco industry dollars, where will they find support for their research?

As a research funding agency and as part of the tobacco control community, how can and should TRDRP respond?

TRDRP invites its investigators and all interested researchers to participate in an open Town Hall discussion of these issues and more. TRDRP was encouraged by its Scientific Advisory Committee to hold this discussion to gather feed-back from its stake-holders on this important topic.

The Media & Tobacco Control

Video by UCSF, Tobacco Control Archives

The visual media has played an important role in tobacco control efforts. With funding from TRDRP, the UCSF Library Tobacco Control Archives is now collecting and preserving outstanding examples of media productions. To demonstrate the variety of materials available to tobacco control researchers a 20 minute video sampler was produced for viewing at this annual meeting.

The video sampler covers 23 years: public service announcements starting with the California Proposition 5 campaign of 1978 and ending with this year's California Department of Health Services ads, segments from the famous "Death in the West" (a program about the Marlboro cowboys that was suppressed for several years), and a taste of the rest of the collection.

Altogether, the visual galaxy of Public Service Announcements, workshops, award ceremonies, television news, curriculum materials, performances, tobacco industry promotions, press summaries, law-enforcement and medical presentations in the TCA is an impressive array of research materials newly added to the UCSF Tobacco Control Archives.

The film loop will run continuously on the hour and half-hour in the Stapleton room during afternoon workshop sessions both days.

For further information contact:
Arel Lucas
Project Archivist
Tobacco Control Archives
University of California San Francisco
415/502-6162
FAX: 415/476-4653
http://www.library.ucsf.edu/tobacco/

American Indian Tobacco Education Network

Asian Pacific Islander/Tobacco Education Network

California Black Health Network

California Breast Cancer Research Program

Center for Disease Control & Prevention

Hispanic/Latino Education Network - USC/IPR

National Organization of Tobacco Use Research Funders

Tobacco Control in California

Tobacco-Related Disease Research Program

Universitywide AIDS Research Program

THOMAS J. GLYNN, PH.D.

As Director of Cancer Science and Trends, Dr. Glynn advises the ACS about emerging issues in cancer prevention and control and recommends cancer prevention and control research that is ready for national application. Prior to coming to the ACS, Dr. Glynn was, from 1991 to 1994, Associate Director of the National Cancer Institute's (NCI) Cancer Control Science Program and, from 1991 to 1997, Chief of the NCI's Cancer Control Extramural Research Branch. From 1983 to 1991, he was Research Director for the NCI's Smoking, Tobacco, and Cancer Program. Dr. Glynn has published widely on tobacco use prevention and control, both in the scientific literature and for consumer, professional, and patient education. He has served as Senior Scientific Reviewer for major reports on tobacco and health from the U.S. Surgeon General's office and the World Health Organization and has been active in tobacco control programs in Eastern Europe and India. Dr. Glynn holds a Master of Science degree in Communications Research/ Statistics from Boston University and a Doctoral degree in Psychology from the Catholic University of America in Washington, DC.

RAYNARD S. KINGTON, M.D., PH.D.

Dr. Raynard S. Kington is Associate Director of the National Institutes of Health (NIH) for Behavioral and Social Sciences Research. In this capacity, he directs the NIH Office of Behavioral and Social Sciences Research in the Office of the Director. Prior to coming to NIH, Dr. Kington was Director of the Division of Health Examination Statistics at the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention. In this capacity he also served as Director of the National Health and Nutrition Examination Survey (NHANES). Prior to coming to NCHS, he was a Senior Scientist in the Health Program at RAND. While at RAND, Dr. Kington was a Co-Director of the Drew/RAND Center on Health and Aging, and National Institute on Aging Exploratory Minority Aging Center. Dr. Kington attended the University of Michigan, where he received his B.S. with distinction and his M.D. He subsequently completed his residency in Internal Medicine at Michael Reese Medical Center in Chicago. He was then appointed a Robert Wood Johnson Clinical Scholar at the University of Pennsylvania. While at the University of Pennsylvania, he completed his M.B.A. with distinction and his Ph.D. with a concentration in Health Policy and Economics at the Wharton School and was awarded a Fontaine Fellowship. He is board-certified in Internal Medicine, Geriatric Medicine, and Public Health and Preventive Medicine.

Dr. Kington's research has focused on the relationships between race, socioeconomic position, and health status, especially in older populations. His research has included studies of the determinants of health care services utilization; the economic impact of health care expenditures among the elderly; and racial and ethnic diffrences in the use of long-term care.

SCOTT J. LEISCHOW, PH.D.

Dr. Leischow became Chief of the Tobacco Control Research Branch in the Behavioral Research Program, Division of Cancer Control and Population Sciences at NCI in July 2000. Prior to taking the NCI position, Dr. Leischow was an Associate Professor of Public Health at the College of Public Health, University of Arizona, and the Director of the Arizona Program for Nicotine and Tobacco Research. His research interests have been focused on the areas of nicotine behavioral pharmacology, tobacco cessation, and the translation of clinical smoking cessation research into community practice. In addition to conducting seminal clinical research studies evaluating the safety and efficacy of potential smoking cessation medications, Dr. Leischow also played a senior role in the development of several statewide tobacco treatment and evaluation programs in Arizona, including the creation of the Arizona Smokers Helpline. In 1998, he was named Arizona Prevention Center Researcher of the Year. He holds an undergraduate degree in Psychology from the University of Wisconsin – Parkside, and a Ph.D. in Health Education from the University of Maryland at College Park.

KATHY SANDERS-PHILLIPS, PH.D.

Kathy Sanders-Phillips is a developmental psychologist who received her Ph.D. in experimental psychology from The Johns Hopkins University. She is currently the Distinguished Scientist in Drug Abuse Research and Director of the Research program in the Epidemiology and Prevention of Drug Abuse at Howard University. She also holds an appointment as Associate Professor in the School of Public Health at U.C. Berkeley. Dr. Sanders-Phillips has published widely in the area of substance abuse with particular emphasis on the impact of exposure to community violence on substance use in African American women and Latinas. She is a member of the National Council for the National Institute on Drug Abuse and the Scientific Advisory Board for the Tobacco-Related Disease Research Program.

DAVID R. WILLIAMS, PH.D.

David R. Williams is a Professor of Sociology, a Senior Research Scientist at the Institute for Social Research, and a Faculty Associate in the African American Mental Health Research Center and the Center for Afro American and African Studies at the University of Michigan. Previously, he was an Associate Professor of Sociology, Yale University, and Associate Professor of Public Health, Yale School of Medicine. He received an MPH from Loma Linda University and a PhD in Sociology from the University of Michigan. Dr. Williams is the author of more than 100 scholarly papers in academic journals and edited collections and a reviewer for some 35 scientific journals. Currently, he is on the editorial board of five scientific journals. He is centrally interested in the determinants of socioeconomic and racial differences in mental and physical health. His research has examined the extent to which social and psychological factors, ranging from stress, racism, social support, and religious behavior, to psychological resources and health behaviors, are linked to social status, and may explain socioeconomic and racial variations in health. He has received numerous awards, including an Investigator Award in Health Policy Research from the Robert Wood Johnson Foundation. He has served on several committees at the national level including scientific panels of the National Academy of Sciences, the Department of Health and Human Services' National Committee on Vital and Health Statistics (and chair of its subcommittee on Minority and Other Special Populations), and the National Science Foundation's Board of Overseers for the General Social Survey. He has also held elected positions in professional organizations, such as the Secretary-Treasurer of the Medical Sociology Section of the American Sociological Association. Currently, he is a member of the Institute of Medicine Committee on Understanding and Eliminating Racial and Ethnic Disparities in Health Care and the MacArthur Foundation.

ANNA H. WU, PH.D.

Anna H. Wu, Ph.D, is a Professor of Preventive Medicine at the University of Southern California. She received her BA degree from the University of California at Berkeley and her Doctorate in Public Health from the University of California, Los Angeles. Dr. Wu's research activities include tobacco-related cancer sites such as lung, stomach, esophagus, and colon. In addition, she has a long-standing interest in the changing cancer patterns of Asian migrants and has an active research program to investigate the role of hormones and diet in the etiology of breast, ovarian and prostate cancers.

NOLAN ZANE, PH.D

Nolan Zane, Ph.D., is Director of the National Research Center on Asian American Mental Health and Associate Professor of Psychology and Asian American Studies at the University of California, Davis. Dr. Zane received his bachelor's degree from Stanford University and his doctorate in clinical psychology from the University of Washington. His research interests include the development and evaluation of culturally based treatments for Asian and other ethnic minority clients, change mechanisms in mental health interventions, program evaluation of substance abuse and mental health programs, and the cultural determinants of addictive behaviors among Asians. He has authored numerous articles on Asian American mental health treatment and services, cultural differences in intra- and interpersonal dynamics (e.g., self-consciousness, assertion), and addictive behavior patterns in Asian communities. He also has co-edited books on Asian American health issues (Confronting Critical Health Issues of Asian and Pacific Islander Americans) and on the psychology of Asian Americans (Handbook of Asian American Psychology). He has served as a consultant on research strategies for culturally-diverse populations for the National Institute on Drug Abuse, the National Institute of Mental Health, the Center for Substance Abuse Prevention, and the Agency for Health Care Policy and Research. His current research examines cultural differences in the role of loss of face in interpersonal relationships with a special focus on client and care provider interactions.

POSTER PRESENTATIONS

A1

Tobacco exposure during pregnancy and its effect on aneuploidy in newborns

Zamora, Frederick G.[1], Ramsey, Marilyn J.[1], Sorensen, Karen J.[1], Christian, Allen T.[1], Bigbee, William L.[2,3,4], Harger, Gail F.[3], and Tucker, James D.[1], Bennett, L. Michelle[1]
Lawrence Livermore National Laboratory

Our laboratory is studying the consequences of maternal cigarette smoking during pregnancy on both the mother and the newborn. Smoking during pregnancy is associated with low newborn birth weight and sudden infant death syndrome. We have preliminary data indicating that exposure to tobacco during pregnancy induces chromosome damage in newborns. We hypothesize that tobacco exposure during pregnancy is associated with increased aneuploidy in newborns.

In this project we are using existing paired newborn and maternal blood samples for which we have active and passive tobacco exposure history during pregnancy. Our long term goal is to determine if chromosomes 13, 18, 21, X and Y are aneuploid more frequently in newborns that were exposed to tobacco during gestation compared to those who were unexposed. These chromosomes were chosen for analysis because they cause birth defects such as Down's Syndrome.

Our short term goal is to establish a protocol to test for aneuploidy. We are preparing DNA hybridization probes to visualize and identify specific chromosomes in interphase cells. The probes are labeled with fluorescent dyes which enable us to use fluorescent microscopy to identify aneuploid cells. To aid in the analysis of probe-labeled slides we are developing a computer program to quantitate the number of cells on a slide as well as the number of the labeled chromosomes within those cells. The frequencies of aneuploid cells in tobacco exposed subjects will be compared to unexposed subjects. We will present preliminary data demonstrating our ability to detect aneuploidy.

Over the next year we will continue to refine and standardize these techniques in order to analyze the existing maternal and newborn samples. Using the results from this study we will be able to further our understanding of the effects that tobacco smoke has on the developing fetus.

TRDRP grant #8RT-0070 Cornelius Hopper Diversity Award Supplement to FGZ. This work was performed under the auspices of the U.S. Department of Energy by the University of California, Lawrence Livermore National Laboratory under contract No. W-7405-ENG-48.

A2

Smoking During Pregnancy: Chromosome Damage in Mothers and Newborns

Bennett, L.Michelle[1], Ramsey, Marilyn J.[1], Bigbee, William L.[2,3,4], Harger, Gail F.[3], and Tucker, James D.[1]
Lawrence Livermore National Laboratory

The consequences of maternal cigarette smoking during pregnancy on both the mother and newborn are being studied. It is of particular interest to understand how smoking and inherent genetic susceptibility relate to observed chromosomal aberrations in circulating blood cells. Approximately one quarter of the population is inherently susceptible to chromosomal damage whereas the remaining three quarters are relatively resistant. It is hypothesized that sensitive populations of newborns and mothers are at increased risk to chromosomal damage by maternal smoking during pregnancy compared to relatively resistant populations.

Blood samples from 300 mothers and their newborns are being collected for this study. Peripheral blood lymphocytes from the mother and the fetal side of the placenta are cultured and harvested 48 and 72 hours later to evaluate chromosomal aberrations and genetic susceptibility, respectively. Chromosome aberrations are detected using whole chromosome painting probes to visualize chromosomes 1, 2, and 4 in red and 3, 5 and 6 in green. Approximately 1000 cell equivalents (~1800 metaphase cells) are scored from each maternal and newborn sample to identify stable and unstable chromosome damage. The clastogen, bleomycin, is used to assess susceptibility to induced chromosomal damage*in vitro*.

In addition to baseline and postpartum interview questionnaires data about smoking history, maternal and newborn blood samples are being tested for two biochemical measures of tobacco exposure. The quantification of cotinine levels and 4-aminobiphenyl-hemoglobin (4-ABP-Hb) adducts will reduce the risk of potential recall bias for self-reported tobacco use. Preliminary data indicate that self-reported cigarette smoking behavior prior to and early in pregnancy are highly correlated with these biochemical measures of exposure.

To date, 170 mother/newborn blood sample pairs have been analyzed for chromosomal damage: 97 are from Caucasian-Americans and 73 are from African-Americans. Sociodemographic data have been collected from all subjects. The distribution of bleomycin-induced chromatid damage in both the maternal and newborn populations deviates from a normal distribution. In general, the newborn lymphocytes are more resistant to bleomycin-induced damage than the maternal cells. The most recent analyses of the data evaluated the effect of age, race, maternal smoking during pregnancy, ever smoking, passive smoking, and bleomycin sensitivity on chromosome aberration frequency. In univariate analyses, there are significant associations between maternal chromosome aberration frequencies and mother's age ($p = 0.05$) and passive smoke exposure ($p = .01$) and these factors remain significant in multivariate analysis. In univariate analyses of data for newborn samples, bleomycin sensitivity associates significantly with chromosome damage. In a multivariate analysis, ever smoking, smoking during pregnancy, and passive smoke exposure are significantly associated with chromosome damage.

In the next year we will finish collecting and analyzing the samples. We will determine if maternal and newborn populations, genetically susceptible to DNA damage, are at increased risk of chromosomal aberrations due to tobacco exposure during pregnancy. The identification of risks associated with maternal smoking during pregnancy are critical for the improvement of the health of the individual and the community.

TRDRP grant #8RT-0070 to JDT and NIH grant R01 HD33016 to WLB. This work was performed under the auspices of the U.S. Department of Energy by the University of California, Lawrence Livermore National Laboratory under contract No. W-7405-ENG-48.

A3

Enviromental tobacco smoke exposure and adverse pregnacy outcomes

Kharrazi, Martin
California Department of Health Services and Public Health Institute

The main objective of this study is to accurately determine the magnitude of association between exposure to environmental tobacco smoke (ETS) in mid-pregnancy and various adverse pregnancy outcomes. Previous studies have been hampered by poor exposure assessment. Questionnaire studies have been hindered by questions that were not comprehensive, and have been limited by the inability of most people to quantify their exposure to ETS. Biomarker studies have only been able to quantify exposure in those women most highly exposed to ETS because of the high limits of assay detection. As a result, both types of studies have misclassified sizeable portions of the study populations in the referent ("unexposed") group, many of whom are exposed to ETS. If there is a true effect of ETS on pregnancy outcomes, then the magnitude of this effect would be diminished in these previous studies.

In this study, we quantified the magnitude of the association of ETS across a large range of exposure with measures of gestational duration, fetal growth and mortality using a sensitive isotope-dilution high performance liquid chromatographic/atmospheric-pressure ionization tandem mass spectrometric cotinine assay (detection limit=0.05 ng/mL serum). The study population consisted of 2,777 woman-infant and 19 woman-fetal death pairs from 11 counties who enrolled in April 1992 in California's prenatal screening program at 15-19 weeks gestation. Serum leftover from screening was banked and cotinine analyzed and only those women with cotinine levels below 10 ng (i.e., nonsmokers) were included. In multivariate analyses, log cotinine was not associated with mean gestational age, but there was a 2.1-fold increase (p=0.09) in the odds of delivery before 37 weeks over the total range of log cotinine values. A dose response effect was found between log cotinine and mean birth weight (-110g, p=0.04) over the range of log cotinine values after controlling for gestational age and five covariates. This effect on growth translated into a 2.5-fold increase (p=0.09) in the odds of low birth weight over the range of log cotinine values. Similar dose-response effects were seen for infant length and head circumference, but not for child's body mass index or brain: body weight ratio, suggesting that ETS-related growth restriction may be proportionate. There was a 3.4-fold increase (p=0.16) in the odds of fetal death over the range of log cotinine values. To summarize the impact of ETS across the continuum of pregnancy, an index of three adverse pregnancy outcomes, including fetal death, low birth weight and preterm birth, was created. The odds of an adverse pregnancy outcome increased 2.4 times (p=0.01) over the range of log cotinine values in multivariate analysis. These effect sizes generally are larger than previously reported.

In the future, we will search for population subgroups that may be more susceptible to the effects of ETS than others, such as certain race and education groups and consumers of caffeine, and estimate the population attributable risk of ETS on adverse pregnancy outcomes. This information will aid in formulating adequate policies and strategies to prevent or minimize tobacco exposure and thus protect fetal growth.

A4

In contrast to the effect of blood cholesterol, smoking is associated with echogenic thickening of the arterial wall. The Los Angeles Atherosclerosis Study

Wu H, Dwyer KM, Shircore AM, Dwyer JH.
University of Southern California

This study focuses on relations between cigarette smoking and the pathophysiology of atherosclerosis in the carotid artery wall. More dense tissue, such as muscle and fibers, produces a stronger echo of sound energy emitted from an ultrasound transducer. This is termed echogenic tissue. In contrast, low density material such as blood and lipid yields weak echos (termed echolucent). Data for this study came from B-mode ultrasonography of the common carotid arteries, blood samples and lifestyle questionnaires collected from a cohort of 281 participants (41% women) aged 40 to 60 years with intima-media thickness (IMT) greater than 0.65 mm in at least one of the two common carotid arteries (indicating the presence of early atherosclerosis). Participants were free of diagnosed cardiovascular disease at baseline and had been recruited for the Los Angeles Arteriosclerosis Study. There were 56 current smokers and 95 former smokers in the cohort. Ultrasonic images were analyzed for IMT and thickness of the echogenic layer (EL) of the intima-media complex. After adjustment for age, sex, plasma lipids and blood pressure in a regression model, a significant increase in EL was observed among current smokers compared to never smokers ($p<0.01$). The echogenic percentage of the intima-media complex (%EL =100 EL/IMT) in current smokers was also greater than in never smokers (difference = 2.47%; 95% CI= 0.03 to 4.92%; $p<0.05$). No increase in %EL was observed among former smokers (p for difference from never smokers=0.6). In contrast, the ratio of total cholesterol to HDL cholesterol (Chol/HDL) was inversely related to %EL ($p<0.05$) after adjustment for smoking status, age and sex. Thus, increased Chol/HDL was associated with greater echolucency of the arterial wall. These findings suggest that while both smoking and elevated blood cholesterol lead to atherosclerotic thickening of the arterial wall, smoking achieves this effect via a somewhat different pathway, perhaps involving more connective tissue and smooth muscle proliferation.

A5

Role of active smoking in subclinical atherosclerosis in Type 2 Diabetics

Mack, Wendy
University of Southern California

Because of micro- and macrovascular complications, cardiovascular-related events are the primary cause of morbidity and mortality in persons with diabetes. We have shown among non-diabetic subjects that both active smoking and exposure to environmental tobacco smoke (ETS) has deleterious effects on measures of subclinical atherosclerosis, including thickening of the arterial wall and increases in stiffness of the arteries. The relationship between tobacco exposures and atherosclerosis in diabetic populations has not been well studied. However, it has been suggested that active smoking may have more deleterious effects on atherosclerosis and cardiovascular outcomes in diabetics compared to non-diabetics.

We used data from a clinical trial conducted among 299 adults (91% Hispanic) with non-insulin dependent diabetes mellitus (NIDDM, or type 2 diabetes). This trial tested the effects of troglitazone, an insulin-sensitizing agent vs. placebo on the progression of atherosclerosis. The primary measure of atherosclerosis measured in this trial was the carotid artery intima-media thickness (IMT) by carotid ultrasonography performed at baseline and every 6 months during the 2-year trial period.

A total of 299 subjects with type 2 diabetes were recruited into this trial (average age = 52 years, 66% female). In contrast to data observed in non-diabetic populations, there was no difference in carotid artery IMT by gender. Adjusting for age and systolic blood pressure, subjects with type 2 diabetes who had ever smoked had a higher mean ± SEM carotid artery IMT (0.88 ± 0.009 mm) compared to subjects who had never smoked (0.84 ± 0.012 mm) ($p = 0.006$). Relative to never smokers, IMT was increased in both current and ex-smokers. A significant linear correlation between carotid IMT and years of smoking was significant among all subjects ($r = 0.19$, $p = 0.001$). Subsequent analyses suggested that the association with smoking and carotid artery IMT was stronger in subjects with higher blood pressure, pulse rate, LDL-cholesterol, and age. The association was not modified by gender, or by indicators of diabetic status such as glycosylated hemoglobin, fasting glucose, or insulin\dose.

These data contrast with similar data obtained in 993 non-diabetic subjects (mean age 56 years, 52% female). Adjusting for age and gender, subjects who had ever smoked (mean IMT = 0.76 ± 0.006 mm) had thicker IMTs than never smokers (mean IMT = 0.74 ± 0.005 mm) ($p = 0.02$). Our data from these two populations suggest that active smoking may have a stronger effect on subclinical atherosclerosis measured by IMT in persons with type 2 diabetes compared to non-diabetics.

A6

Early Benefits of smoking cessation in young adults

Barth, Jacques D.
Southern California Prevention and Research Center (SPARC)

Smoking cessation methods in a young adult working population is poorly understood. Access to this group is difficult as no specific contact procedures are in place. The long-term impact (2-3 years) and cessation on vascular viability is unknown. This population (17-21 years) was studied for 24 months for endothelial function (flow mediated dilation; FMD) and carotid intima media thickness (QIMT) using sonographic procedures. Offline quantitative assessment was done using the ARTIS® computerized software technique. Participants were matched for age and gender. At 24 months 120 cases remained (average 20.7 years); 56 smokers and 64 non-smokers.18 smokers had quit (10 women, 8 men) and 2 men had started. At month 24 the results were: Smokers showed a significantly thickened QIMT and a endothelial dysfunction. The smoking quitters showed, already after 2 years, FMD and QIMT values more compatible with non-smokers. The potential for smoking cessation programs at this susceptible age category need to be applied. Results:

Smokers (N=40)	**Ex-Smokers** (N=18)	**Non-smokers** (N=62)
FMD (d %)		
3.2 ± 2.9 **	8.2 ± 3.1	9.8 ± 3.8
QIMT (µm)		
651± 013	598 ± 024	540 ± 022**

Findings at 24 months; **p<0.01;
Average age 20.7 years

A7

Physicians' advice to quit smoking: results from the 1996 and 1999 California Tobacco Control Surveys

*Burns, David M., M.D., Reed, Mark B., Ph.D., Major, Jacqueline M., M.S.
University of California, San Diego

Approximately 70% of all smokers in the United States visit a physician each year. This represents a unique opportunity for physicians to reach millions of smokers with brief smoking cessation advice. Many clinical trial interventions examining the efficacy of physicians' advice have shown that brief smoking advice increases quit rates and is very cost effective relative to other more intensive smoking cessation interventions. The purpose of this project is to examine physicians' advice in California using population-based survey data. There are three primary goals of this research: 1) examine the prevalence of physicians' advice in California, 2) determine if physicians' advice has increased over time in California and 3) examine the effect of physicians' advice on cessation activity, cessation attempts and cessation success.

For this research we are using data from the 1996 and 1999 California Tobacco Surveys. For both survey years, current and recent former smokers (defined as abstinence of 12 months or less) were asked to indicate the number of times they visited a physician during the past year. Respondents with at least one visit to the doctor were asked if a physician had advised them to quit smoking during the health care visit. Respondents were also asked questions concerning smoking cessation behavior as well as several demographic questions.

To date, we have examined the prevalence of seeing a physician in California, the prevalence of receiving physicians' advice and the effect of physicians' advice on cessation. We used multiple logistic regression modeling to examine the demographic determinants of seeing a physician and receiving advice in 1996 and 1999 as well as to determine if the rates of seeing a physician and receiving advice increased between both survey periods. Cessation outcomes were also modeled so that we could determine the effect of physicians' advice on cessation activity, cessation attempts and cessation success in 1996 and 1999.

The results showed significant increases in both seeing a physician and receiving advice between the 1996 and 1999 CTS. In 1996, physicians' advice influenced both cessation activity and cessation attempts but had no effect on long-term cessation. In 1999, physicians' advice had no effect on any measure of smoking cessation. Our next set of analyses will examine whether cigarette price increases occurring at the end of 1998 and in 1999 increased smoking cessation among the 1999 CTS respondents, resulting in the attenuated affect of physicians' advice on cessation observed in 1999.

As demonstrated in numerous clinical trial intervention studies, physicians' advice can increase long-term smoking cessation rates among smokers. The results of our research, however, suggest that physicians' advice does not appear to have a substantive effect on population levels of cessation success in California. Achieving the results observed in clinical trial studies will require changes in medical office systems, organizational policies and changes in physician behavior. *Principal Investigator

A8

Trends of adolescent 30-day smoking in California from 1990 to 2000: An age-period-cohort analysis

Chen, Xinguang PhD., Liu, Xiaowei M.S.
University of Southern California

Objectives: This study analyzed age, period and cohort effects on secular trends in cigarette smoking among Californian Adolescents from 1990 to 2000.

Methods: Study subjects were 28,971 adolescents (50.5% males) 12 through 17 years of age from the California Tobacco Survey (youth part) and the California Youth Tobacco Survey. These subjects were from randomly selected households representing the state population. 30-day cigarette smoking was used as outcome measure and prevalence rate of 30-day smoking was computed as an indication of smoking levels for trend measurement. Effects from chronological age, historical time period and birth cohort were analyzed using the age-period-cohort modeling method.

Results: The 30-day smoking prevalence rates for adolescent males and females were 10.6% and 9.4% in 1990 respectively. They increased to 11.3% and 11.9% in 1996 before leveled off. The prevalence rates declined since 1997 and reached to 7.9% for males and 6.0% for females in 2000. An increase in risk of smoking over time for cohorts born before 1978 (a cohort effect) is associated with the increasing trend in 30-day smoking from 1992 to 1996. A decline in risk of smoking over time for the period from 71997 to 2000 (a period effect) and a decline in risk of smoking over time for the cohorts born since 1978 (a cohort effect) are associated with the decreasing trend in 30-day smoking.

Conclusions: An increased risk of smoking over time for adolescents born during 1974 ~ 1978 period attributed to the increasing trend of 30-day smoking prevalence during the 1990 –1996 period in California. Tobacco control program in California reduces adolescent smoking by protecting adolescents 12 years of age and younger from smoking when they advance from children to adolescents during the program period. It is recommended that the current tobacco control efforts be continued for long term successful smoking free California.

A9

Patterns and risk factors for adolescent smoking progression

Li, Chaoyang
University of California, Los Angeles

Tobacco use remains the leading preventable cause of death and disease in the United States. Despite increased public health knowledge about the adverse health effects of smoking, adolescents still experiment with tobacco use. While there has been a slight decline nationally in adolescent smoking in 2001, the major progression of new smokers has been and continued to be adolescents. Thus, identifying different patterns of smoking progression is an important issue because various developmental patterns may be linked to different etiological pathways. The objectives of this research were: (a) to examine patterns of smoking progression among California adolescents by gender and ethnicity; (b) to determine the relative importance of social, psychobehavioral, and demographic influences in predicting smoking progressions; and (c) to test potential mediating and moderating mechanisms of predictors smoking progression.

The present research utilized the longitudinal data from the Tobacco Program and Policy Trial project conducted among junior high school students in Orange County, California between 1997 and 2000. A total of 2,053 subjects who completed all three-wave surveys were analyzed in this study. The longitudinal sample comprises of 49.8% males, 39.9% whites, 27.2% Hispanics, 16.2% Asians, 2.3% African Americans.

The results showed that in general there was significant increase of prevalence rates of lifetime smoking (from 16% to 30%) and current smoking (from 3.2% to 7.2%) from seventh grade to eighth grade. The prevalence rates of smoking were higher in males, Hispanics, African Americans, and those in the control group compared to their counterparts. Overall the proportion of non-smoker latent status was 89% at early seventh grade, 82% at middle seventh grade, and 76% at eighth grade, indicating a more rapid progression of smoking from 7th to 8th grade. Adolescents who had tried or experimented smoking had higher probabilities of progressing toward more advanced smoking stages. Males, adolescents in the control group, and whites had higher risk of transition form lower to higher stages of smoking in general.

Three classes of adolescents were identified based on the patterns of their smoking progressions: stable non-smokers (69.2%), slow escalators (28.4%), and stable smokers (2.3%). Diverse patterns of smoking progression were identified in different genders, program groups, and ethnic populations. Nearly half of the total program effects on the reduction of lifetime smoking were mediated through altering intention to smoke. Friend's smoking interacted with refusal self-efficacy in that adolescents who had higher refusal were less influenced by friend's influence on their own smoking. Male gender, intention to smoke, and friend's smoking were significantly associated with greater risk of regular/addictive smoking.

The findings of this research enhance our understanding of gender and ethnic differences of smoking progression and related risk factors in California adolescents. It suggests that enhanced school non-smoking policy may reduce the probability of initiation and progression of adolescent smoking. Variables such as intention to smoke, refusal self-efficacy, and friend's smoking can be emphasized in the smoking prevention programs.

A10

Do adolescents discriminate among types of smokers and related risks?

Halpern-Felsher, Bonnie L.
University of California, San Francisco

The ultimate goal of this TRDRP-funded research is to inform and improve programs that attempt to reduce or prevent adolescent tobacco use. Following 600 9th graders over three years, this study is examining: 1) the influence of risk judgments on tobacco use onset; 2) the relationship between the onset of tobacco use and subsequent risk judgments; 3) whether experiences with tobacco-related outcomes influence subsequent risk judgments and tobacco use; 4) how vicarious exposure to tobacco use influence risk judgments and tobacco use; and 5) whether the relationship between risk perceptions and behavior varies by gender and race/ethnicity. Prior to conducting this larger study, we conducted a pilot study to examine whether 1) adolescents discriminate among categories of smokers, 2) adolescents discriminate based on frequency and/or quantity, 3) these discriminations engender different perceptions of risk attributes to smoking, and 4) these categories affect adolescents' perceptions about smokers' ability to quit smoking. This pilot study was conducted for several reasons: First, many studies concerning smoking and smoking-related outcomes among adolescents use categories such as *casual* or *regular* smoker to define different types of smokers. Unfortunately, there is no consistency in how these categories are defined across studies. Second, it is not clear whether adolescents themselves differentiate between different types of smokers and, if so, the basis on which such discriminations are made. Finally, the results of this pilot study informed the development of risk scenarios used in the larger longitudinal study.

Five hundred and fifty 9th graders (mean age 14) who never smoked completed the self-administered survey. Subjects were asked to define four pre-selected categories (non-smoker, casual smoker, smoker, and addicted smoker) based on both quantity of cigarettes smoked and frequency of smoking. Subjects also assigned a percent risk for four smoking related outcomes (lung cancer, frequent colds, heart attack, difficulty exercising) to each category of smoker. Finally, subjects were asked to assign a percent chance of quitting for each type of smoker. Results indicated that adolescents discriminated significantly among non-smokers, casual smokers, smokers and addicted smokers, based on both frequency of smoking and quantity of cigarettes smoked (Wilk's Lambda =.29, F=5495.76, p=.00; Wilk's Lambda=.60, F=2564.25, p<.00, respectively). Perceptions of risk also showed significant differences, with addicted smokers perceived as having the greatest chance of experiencing each negative outcome, followed by the smoker, the casual smoker and finally the non-smoker (p<.000). Finally, adolescents ascribed a far greater chance of quitting smoking to casual smokers than they did to either regular or addicted smokers (41% vs. 27% vs. 19%; p<.000). Understanding how adolescents discriminate among categories of smokers has important implications for smoking-related interventions and risk communication. Distinctions between casual and regular smokers are particularly problematic, based on evidence that casual use typically becomes regular use. Patterns of beliefs about different types of smokers suggest that caution be exercised in how we communicate about smoking to this age group.

A11

Is emotional intelligence protective against psychosocial risk factors for smoking in early adolescents?

Trinidad, Dennis R., Johnson, C. Anderson, Chou, Chih-Ping, Unger, Jennifer, B., Azen, Stanley P.
University of Southern California

The goal of the current project is to determine whether high emotional intelligence (EI) may be a protective factor against psychosocial predictors of adolescent smoking. EI may be related to psychosocial predictors and thus may be indirectly tied to adolescent smoking. Though previous work has explored EI's direct association with adolescent smoking, its relation to psychosocial risk factors for smoking has not yet been explored. Psychosocial risk factors of interest include negative social consequences of smoking because it is generally targeted by social-influences based tobacco prevention programs, and susceptibility to smoking and refusal self-efficacy as both variables have been shown in past research to be predictors of future smoking behaviors. EI is defined as the ability to: accurately perceive, appraise, and express emotion; access and/or generate feelings in facilitating thought; understand emotion and emotional knowledge; and regulate emotions. To assess the EI, a shortened version of the Multifactor Emotional Intelligence Scale, Adolescent Version (Mayer, Salovey & Caruso, 1997b), was administered to 416 healthy 6th grade students (53% male) from middle schools in the Los Angeles area (mean age=11.3 yrs; 32% Latino, 29% Asian/Pacific Islander, 13% White, 19% Multiethnic, 6% Other). Students also completed a self-administered survey assessing smoking related variables, including demographics, attitudes, beliefs, behaviors and cultural factors.

Regression models controlling for age, gender, ethnicity, acculturation, socioeconomic status, grades received in school, perceived social norms of smoking, and perceived peer attitudes toward smoking indicate that emotional intelligence is protective against the aforementioned psychosocial risk factors for smoking in early adolescents. Specifically, multiple regression analyses revealed that those with high emotional intelligence perceived more negative social consequences of smoking ($p<0.01$). Logistic regression models fit for the dichotomous outcome variables (susceptibility to smoking and refusal self-efficacy) revealed that, relative to those with low EI, those with high EI were less susceptible to smoking in the next year (OR=0.35; 95% CI: 0.13-0.97; p=0.04), and more efficacious in refusing cigarette offers (OR=0.62; 95% CI: 0.39-0.97; p=0.04).

Though results indicate that high EI is a protective factor for these smoking precursors in adolescents and should be considered when designing prevention programs, further analyses need to be conducted to better understand the role of EI in the relationship between psychosocial risk factors and smoking in adolescents. For example, does EI moderate the relationship between negative social consequences for smoking and one's susceptibility to smoking? Future adolescent smoking prevention programs may thus be improved by incorporating aspects of emotional intelligence.

A12

Evidence of peer influences as a mediator of the relationship between depression and smoking initiation in young adolescents

*Ritt-Olson, Anamara , Unger, Jennifer, Ph.D., Sussman, Steve , Ph.D., Johnson, C. Anderson, Ph.D., & Nezami, Elahe, Ph.D.
University of Southern California

Depressive symptoms have been shown to be predictive of smoking initiation. Patton and colleagues (1998) found that peers were instrumental in understanding the relationship between depression and smoking. Depression may make teens more susceptible to peer influences. This study explores peer influences as a mediator of the relationship between depressive symptoms and smoking. Over 800 seventh graders in the Los Angels area participated in this cross-sectional analyses and completed measures of depressive symptoms (CES-D), ever smoking, and peer influences. The ethnic background of participants were 37% white, 30% Latino, 21% Asian, 7 % Other, 6% Multi-Ethnic. Depressive symptoms and peer influences were predictive of ever smoking when entered singly into a model with ethnicity and gender as covariates; depression standardized Beta = .19, $p<.001$ and peer influences STB = .59, $p<.001$. Evidence was found that peer influences fully mediate the association between depression and smoking; standardized beta depression with peer influences in the model = .08, p = ns. Because Latinos had significantly higher levels of depression and peer influences, the mediated model was tested on Latinos only. Both direct (STB = .21, $p<.01$) and indirect pathways remained significant (STB = .18, $p<.05$), suggesting a partially mediated model. When this same model was tested with Asians only, who had the lowest levels of depressive symptoms, only the indirect pathways were significant. These cross-sectional results suggest that future longitudinal studies should address the influences of peers and ethnicity on the relationship between depressive symptoms and smoking.

A13

Differences in smoking behaviors among bullies, victims, and bully-victims among California 6th grade students

Mouttapa, Michele, MA, Gallaher, Peggy, PhD, and Unger, Jennifer, PhD
University of Southern California

Bullying is a form of aggressive behavior that occurs frequently in schools worldwide. The Kaiser Family Foundation (2000) found that children aged 8 to 15 years considered bullying a "big problem" that ranks higher than racism, AIDS, and peer pressure to use drugs and alcohol. Two major classifications of bullying include direct bullying (i.e., physical and verbal assaults) and indirect bullying (i.e., shunning and rumor-spreading).

There is some evidence that bullies (Berthold & Hoover, 2000), and victims (Sussman and Dent, 2000) both have higher rates of smoking compared to other students. There is, however, a lack of literature that has compared smoking rates between bullies, victims, bully-victims (student who are both bullies and victims), and other students' risk for smoking. Furthermore, no known studies have examined the differential effects of direct and indirect bullying on smoking.

The purpose of this study was to determine whether students classified as Bullies, Victims, and Bully-Victims had higher rates of smoking than children who did not belong to any bullying category (Controls). An ethnically diverse sample of 492 6th graders with parental implied consent completed a self-administered survey that included measures of bullying and smoking behaviors. 64.4% of the sample was female, and their mean age was 11.3 years. Controlling for the effects of friends' smoking, separate odds ratios were calculated for boys and girls on direct and indirect forms of bullying. Logistic regression results revealed that among boys, Direct Bullies had higher rates of smoking than Controls (RR= 5.0). Boys who were Indirect Bullies (RR= 3.6) or Indirect Bully-Victims (RR= 3.9) had higher rates of smoking than Controls. Among girls, Direct Bully-Victims had higher rates of smoking than Controls (RR= 5.0). None of the indirect bullying categories were significant predictors of smoking among girls.

These findings suggest that adolescent Bullies and Bully-Victims are at greater risk of smoking compared to Victims and Controls. These effects varied by gender and type of bullying. Longitudinal studies would enable researchers to better understand the causal relationship between bullying and smoking through childhood into young adulthood. Preventing smoking and bullying behaviors in a social skills training program would be a cost effective intervention strategy. To test the feasibility of a dual-targeted program, future longitudinal studies should examine whether social skills training is related to lower rates of subsequent smoking and bullying.

A14

Factors influencing smoking behavior: california twin program

Ann S. Hamilton, Myles G. Cockburn, and Thomas M. Mack.
University of Southern California

The California Twin Cohort consists of a population-based cohort of twins born in California who have completed a risk factor questionnaire. Currently, nearly 35,000 pairs are represented in the cohort. Information on personal smoking as well an exposure to environmental tobacco smoke was obtained. In this cohort we have assessed the role of some shared familial and personal factors on the risk of ever smoking.

Preliminary analyses have shown that among those pairs born before 1950 both twins ever smoked in 48% of the like-sex male pairs compared to 33% of like-sex female pairs. Among those born in 1950 or later these percentages were reduced to 31% among male pairs and 28% among female pairs. This proportion did not vary by zygosity; however, the proportion of pairs in which both twins never smoked was higher in the identical pairs of both sexes in comparison to the fraternal pairs. In a multivariate analysis, older birth cohort and parental smoking increased risk of ever smoking (OR's=1.4-1.7) while personal education beyond high school was protective (OR=0.5). However the largest predictor of ever smoking in both zygosity groups was whether or not the co-twin smoked and the adjusted OR was 3X higher in the identical pairs than in the fraternal pairs (OR's for MZ=13-16; OR's for DZ=4-5). These findings indicate that shared environmental factors had a modest effect on smoking initiation while the most important factor was whether or not the co-twin smoked. The much higher OR's for the MZ twins may imply that genetic factors are playing a role; however increased peer influence and more similar environmental factors may also be involved. Additional factors related to smoking behavior are being studied and the analysis will be extended to the complete data set.

B1

Nociceptor spinal terminals are targets for nicotine to suppress inflammation

Jia.-Pei. Miao, Frederick
University of California, San Francisco

Nicotine acts at the spinal cord to dose-dependently inhibit bradykinin-induced plasma extravasation in the knee joint of the rat. The goal of the present study is to determine the target for the action of nicotine.

To address this question we compared the actions of intrathecal nicotine with that of capsaicin, a known stimulator for nociceptors, and by using the blockers of spinal primary afferent neurotransmitters and spinal descending antinociceptive pathways. We found that spinal administration of blockers for primary afferent neurotransmitters, RP-67,580 (a NK-1 receptor antagonist) or AP-5 (a NMDA receptor antagonist), markedly attenuates the inhibition of bradykinin-induced plasma extravasation by either intrathecal nicotine or intraplantar capsaicin. Conversely, intrathecal administration of phentolamine (an ?-adrenoceptor antagonist) or naloxone (an opioid receptor antagonist), both block descending antinociceptive controls, enhances the inhibitory action of either intrathecal nicotine or intraplantar capsaicin. These observations indicate that neurotransmitters of primary afferents mediate the action of nicotine in a pattern similar to that of capsaicin. Furthermore, the anti-inflammatory action of nicotine, like that of capsaicin, is under modulation by spinal descending pathways. Our findings provide evidence that the central terminal of the primary afferent nociceptor is the spinal target at which nicotine acts to inhibit inflammation.

Based on these and previous findings, we will extend our study to determine: first, the subtypes of the nicotinic receptors which activates the primary afferents and second, the spinal descending mechanism which modulates the nicotine-induced activation of primary afferents. We will focus on the descending mechanism linked to the vagal activities. Results from our preliminary studies suggest that modulatory action of this descending mechanism(s) may be enhanced by stimulation of the vagal afferents electrically or physiologically (by visceral distension). These vagal afferents project to the supraspinal centers, which in turn send modulatory signals to the periphery via spinal descending pathways.

Since nicotine absorbed from tobacco smoking can easily enter the central nervous system including the spinal cord and thus produce anti-inflammatory actions, and since the novel modulatory mechanism(s) we are characterizing can be related to physiological activity of the gut, it is possible that the unwanted action of nicotine could become worse if the intestine does not function properly. Our studies are, therefore, of both physiological and pathophysiological significance.

B2

Nicotine suppression of tastant-evoked neural activity in the rat

Simons, Christopher T.
University of California, Davis

Weight loss associated with tobacco use contributes to the initiation and maintenance of smoking behavior. However, the mechanism by which cigarette smoke or nicotine, its active constituent, leads to weight loss is not fully understood. We propose that nicotine modulates activity in the neural taste pathway such that foods consumed following exposure are deemed less palatable.

Responses to five tastants (NaCl, citric acid, sucrose, glutamate and quinine) were recorded in rat neurons residing in the first central taste nucleus—the solitary nucleus (NTS)—prior to and following pretreatment of the tongue with one of three doses of nicotine (600 mM, 8.7 mM, 0.87 mM) for 4 min. None of the cells tested to date (3 of 3) responded to the lowest dose (0.87 mM) of nicotine. Furthermore, taste responses following nicotine administration were not different from those obtained prior to nicotine. In response to the intermediate nicotine concentration (8.7 mM), 4 of 5 neurons responded with an increase in firing rate. Moreover, following the cessation of nicotine administration, tastant-evoked activity was substantially reduced as compared to pre-nicotine levels. Taste responses recovered to pre-nicotine levels within approximately 6 minutes following the termination of nicotine application. Finally, 5 of 6 neurons responded to the highest dose of nicotine (600 mM) with an increase in firing rate. Following nicotine administration, tastant-evoked activity of these neurons was significantly suppressed but recovered to pre-nicotine levels within approximately 9 minutes.

Two properties associated with nicotine may underlie the suppressive effect of tastant-evoked activity. First, nicotine is an irritant that elicits activity from nociceptive neurons resulting in a sensation of pain. Other irritant chemicals including capsaicin (the pungent principle in chili peppers) and piperine (the pungent principle in black pepper) have been shown to suppress taste responses either electrophysiologically or psychophysically. Alternatively, nicotine is a bitter chemical and previous studies have documented the suppression of non-bitter tastants following the administration of quinine. To date, it is unknown by what mechanism nicotine suppresses tastant-evoked neural activity. Delineating between irritant and bitter properties associated with nicotine as a mechanism for taste suppression remains a goal of our laboratory.

Although the data accumulated to date suggest that nicotine suppresses central taste transmission, it is unknown whether this translates to a suppression of taste intensity as perceived by humans. To address this possibility, psychophysical testing of human subjects will be undertaken to determine if the neurophysiological changes observed presently correlate with human perception. By so doing, human subjects and animal models can be studied simultaneously allowing for a more comprehensive understanding of the mechanisms underlying nicotine-suppression of taste sensations.

Understanding how nicotine affects taste processing can lead to new approaches aimed at reducing weight gain following the cessation of smoking. Because weight gain is a significant factor hindering smokers from quitting, alleviating this unwanted side effect may improve the success rate of smokers who would like to stop.

B3

Proteins involved in nicotinic receptor clustering

Conroy, William G.
University of California, San Diego

Nicotine, the major neuro-active chemical in tobacco, exerts its effects by binding to specific receptor proteins called nicotinic receptors. Nicotinic receptors are found on the surfaces of neurons throughout the nervous system. These receptors normally respond to the neurotransmitter acetylcholine when released at synapses (the sites where signals from one neuron are transferred to the next). Many of the neurons that express nicotinic receptors position the receptors on the neuron in discrete locations or clusters. This compartmentalization of the nicotinic receptors allows for precise activation of subsets of receptors, distinct signaling to the interior of the cell, and separate regulatory control of receptor populations. Thus, how and where the receptors are localized on a neuron determine their function and regulation. The proteins and mechanisms for positioning nicotinic receptors on neurons are not known.

Nicotinic receptors are found on neurons in all autonomic ganglia (clusters of neurons outside the central nervous system). Most of the neurons in these ganglia have at least two classes of nicotinic receptors that differ in their pharmacology, electrophysiological properties, subunit composition, and cellular location. One class of receptors contains α7 subunits and is located outside of synaptic sites on these neurons. The other class of receptors contains α3 subunits in combination with other subunits and is found outside as well as within synaptic sites called postsynaptic densities. Postsynaptic densities are a complex network of proteins on the receiving side of a synapse thought to be involved in organizing and regulating the signaling components necessary for responding to incoming signals.

Recently, families of proteins containing specific protein-interaction domains called PDZ domains have been identified in postsynaptic densities at synapses in the central nervous system where they are implicated in the assembly of glutamate receptors, enzymes, and cytoskeletal components into signaling scaffolds. We report here that one family of PDZ domain proteins may play a similar role in ganglionic neurons, organizing and regulating nicotinic receptors located at postsynaptic densities. We used specific antibodies to PDZ domain proteins in combination with fluorescence microscopy to determine the expression and localization of these proteins on ganglionic neurons. We found these proteins arranged in discrete clusters on the cell bodies of the neurons. Most of the clusters were found together with nicotinic receptors containing α3 subunits. When the neurons were dissociated and grown in cell culture for 1 week the clusters of PDZ domain proteins and nicotinic receptors were found co-clustered on the cell bodies and processes extending from the cells, presumably at sites of newly formed synapses. We are now attempting to determine if the PDZ domain proteins directly interact with the nicotinic receptors.

PDZ domain-containing proteins appear to play key roles in organizing and targeting receptors and effectors at synaptic sites on neurons. We have identified a family of PDZ proteins as candidate proteins for fulfilling these roles for nicotinic receptors. These studies are providing basic information regarding the function and regulation of the receptors that mediate nicotine's effects.

B4

Regulation of nicotinic acetylcholine receptors on rat hippocampal neurons

Zago, Wagner M.; Kawai, Hideki; and Berg, Darwin K.
University of California, San Diego

Nicotine is the primary addictive agent in tobacco driving human behavioral changes that promote tobacco-related disease. Nicotine acts through a class of signaling molecules on neurons called nicotinic acetylcholine receptors (nAChRs) that normally respond to the neurotransmitter acetylcholine. One of the most abundant nAChRs in brain is a species composed of subunits encoded by the α 7 gene. Importantly, α7-nAChRs allow calcium to enter the neuron, thereby regulating a large variety of cellular events. As a result, α7-nAChRs contribute to many brain functions, including learning and memory, and have been implicated in numerous neuropathologies, including Alzheimer's disease.

The hippocampus, which is essential for many kinds of memory formation, contains one of the highest concentrations of α7-nAChRs. We have used a fluorescent marker to examine the distribution and regulation of α7-nAChRs on rat hippocampal neurons grown in dissociated cell culture for 2-3 weeks. The fluorescent marker is a derivative of α-bungarotoxin, a small protein from snake venom and binds tightly and specifically to α7-nAChRs on the cells. We find that α7-nAChRs are expressed at significant levels on most inhibitory neurons, namely neurons that have glutamic acid decarboxylase (GAD), an enzyme required to synthesize the inhibitory neurotransmitter GABA. The α7-nAChRs are arranged in discreet clusters on the dendrites (processes that extend from neurons to receive synapses) and on the cell bodies. Interestingly, the clusters are localized in part at what appear to be inhibitory synapses, namely sites containing GAD on the presynaptic side and $GABA_A$ receptors on the postsynaptic side. The location implies a modulatory role for α7-nAChRs at inhibitory (GABAergic) synapses, consistent with previous physiological findings.

Blockade of neural activity for 3 days, either by using tetrodotoxin to prevent action potentials or glutamate receptor inhibitors (CNQX/APV) to prevent excitatory synaptic transmission (glutamatergic), significantly reduces the proportion of inhibitory neurons expressing detectable α7-nAChRs. Biccuculine, which blocks $GABA_A$ receptors and therefore prevents inhibitory synaptic transmission, has no obvious effect on the number of such cells expressing α7-nAChRs. Treating the cultures for 3 days with either of two secreted proteins, namely brain-derived neurotrophic factor (BDNF) or neuregulin (Nrg-β1), significantly increases the

proportion of inhibitory neurons with high levels of α7-nAChRs. Neither BDNF nor Nrg-β1, however, was able to compensate for either tetrodotoxin- or CNQX/APV-induced decrements in α7-nAChR expression. Preliminary experiments indicate that nicotine at concentrations found in the brains of smokers can increase α7-nAChR levels on the neurons. None of the treatments alter the number of inhibitory neurons in the cultures.

Hippocampal α7-nAChRs can be activated by acetylcholine, choline, and nicotine, but not by GABA. Their localization at GABAergic contacts suggests they modulate rather than mediate inhibitory transmission. The results described here indicate that α7-nAChRs are subject to competing forms of regulation that control their expression on hippocampal neurons. These studies lay the groundwork for determining how chronic exposure to nicotine, resulting from tobacco usage, may alter hippocampal function.

B5

Nicotine and its metabolites: apoptosis in developing neurons

Zhang, Jun
Human BioMolecular Research Institute

During maternal smoking, nicotine readily gains access to the fetal compartment. Based on previous reports on excessive neuronal apoptosis in fetal brain after nicotine exposure during pregnancy, we proposed to evaluate the effects of nicotine and their metabolites, including cotinine, nicotine iminium ions, and nitrosoamines, on apoptosis of developing neurons through the study of biochemical apoptotic events, and understand the biochemical mechanisms of neuronal apoptotic cell death triggered by nicotine.

Our first year of research has been focused on the development of the hippocampal progenitor neuronal culture system and evaluation of their morphological and biochemical changes during neuronal differentiation and nicotine treatment. The hippocampal progenitor neurons culture system was obtained and established in the lab. Differentiation of the progenitor neurons have been monitored for up to 6 days and the morphological changes during differentiation has been examined. Expression profile of neuronal marker proteins NFH and GAD, neuronal precursor marker proteins, vimentin and nestin, apoptosis regulatory proteins, Bcl-xl, Bcl-2, p53, and p21 were evaluated at various differential stages. Morphological changes of undifferentiated and differentiated neurons after nicotine treatment were examined with vital dye. It has been reported that the undifferentiated immortalized hippocampal progenitor cells are very sensitive to low doses of nicotine treatment (0.5 mM) and results in 50% cell death (Berger et al., 1998). However, our repetitive experiments using different concentrations of (–)-nicotine (0.1–100 mM) and different length of treatment time (24–48 hrs) did not show the extensive apoptotic effect of (-)-nicotine as reported previously. Nicotine metabolites, including cotinine, 1,2-, and 1,5-nicotine iminium ion, were successfully chemically synthesized. We did not observe any decrease in cell viability after treatment of the HC2S2 cells with cotinine and iminium ion.

To resolve the controversial results, we have isolated subgroup HC2S2 cell clones by limited dilution. We think that low number of heterogeneous cells from the original cell preparation may have been preferentially enriched during extended culture passage since the previous publication (Hoshimaru et al.1996). We also suspect that extended cell culture may lead to maturation of some population of the progenitor cells based on the expression of adult form GAD in undifferentiated cell population. Such maturation could explain the resistance of this cell population to (–)-nicotine treatment as compared to the original report. Therefore, expression of GAD will be used to identify immature progenitor neuron clones and to eliminate the potential confusions caused by heterogeneous cell population. We will also focus on the primary neuron cell culture systems from early rat embryo for parallel study. In the mean time, overwhelming reports indicated nicotinic receptor-mediated protection against β-amyloid and glutamate neurotoxicity and suggested potential use of nicotine to delay the progress of Alzheimer's disease. These reports again confirmed the linkage of nicotinic receptor activation and neuronal survival status. Our research will further clear the controversial on when nicotine and its metabolite are pro-death and when they are pro-survival.

B6

Interactions between menthol and nicotine in the oral cavity

Carstens, E.
University of California, Davis

Menthol is a common additive in chewing gum, mouthwashes and other products because of the cooling and "fresh" sensations it elicits. Menthol is also commonly added to tobacco products such as mentholated cigarettes or chewing tobacco. The preference that some consumers have for mentholated tobacco products is presumably due a sensory effect of menthol in combination with nicotine and other tobacco constituents, since menthol itself does not act in the central nervous system. We propose two opposing effects of nicotine that might contribute to the acceptance of mentholated tobacco products. On one hand, menthol at higher concentrations elicits an oral irritant sensation[1] that may interact with the irritant sensation of nicotine[2] to produce a "harsh" sensory impact that may be desirable, analogous to a preference for spicy food. On the other hand, menthol-induced irritation may cross-desensitize the oral irritant sensation produced by nicotine, thereby reducing the harsh impact of inhaled smoke (or ingested tobacco) and thus making it more palatable. In the present study we have investigated these two possibilities in controlled psychophysical experiments.

Student and staff volunteers participated in this study which was approved by the UC Davis Human Subjects Committee. In the first experiment, 0.3% (19.2 mM) l-menthol was applied successively to one side of the tongue 10 times at 1-min intervals, and subjects rated the intensity of the perceived irritation using a bipolar category scale. The intensity of irritation progressively decreased across trials, consistent with desensitization. To test for cross-desensitization of nicotine-evoked irritation by menthol, nicotine (0.6 %; 37 mM) was applied to both sides of

the tongue simultaneously, 5 min after the conclusion of menthol application or after the cooling sensation of menthol had subsided. In both cases, nicotine-induced irritation was significantly weaker on the menthol-pretreated side, consistent with cross-desensitization of nicotine-evoked irritation by menthol. Finally, menthol was repeatedly applied to one side of the tongue at a shorter (20-sec) interval, and elicited a rapid increase in irritant sensation over the initial trials, consistent with sensitization, followed in subsequent trials by a progressive reduction in irritation (desensitization). After a 5 min rest period, self-desensitization was confirmed. Repeated application of menthol at the same short interstimulus intervals was then resumed, and resulted in a significant mean increase in irritant intensity consistent with stimulus-induced recovery (SIR).

Thus, application of higher concentrations of menthol alone induces an oral irritant sensation along with cooling. The intensity of irritation evoked by repeated delivery of menthol varied depending on the rate of application, illustrating the complexity of menthol's sensory effects. Importantly, menthol strongly cross-desensitizes irritation evoked by nicotine, in a manner that was independent of menthol's cooling action. The data are therefore consistent with the possibility that menthol may increase the palatability of mentholated tobacco products by reducing the burning sensation elicited by nicotine.

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B7

Nicotine effects on renal function in experimental diabetes

Gabbai, Francis B.
University of California, San Diego

Smoking has been recognized as a major risk factor for the development and progression of kidney disease in patients with both insulin-dependent and non insulin-dependent diabetes mellitus. As a risk factor, smoking 1) increases the risk for the presence of protein in urine, 2) shortens the time interval between onset of diabetes and onset of presence of protein in the urine, 3) accelerates the rate at which patients loss kidney function and require dialysis in order to live. In spite of the major impact of smoking on progression of diabetic renal disease, very little is known about the mechanism(s) by which smoking accelerates renal injury.

Studies performed in our laboratory have investigated the effects of intravenous administration of nicotine (as a surrogate for smoking) on kidney function in normal animals and animals with experimental diabetes mellitus. The studies demonstrate that administration of nicotine is associated with an important increase in hydrostatic pressure in the glomerulus which constitutes the kidney filtering unit. This increase in hydrostatic pressure has been observed both in normal animals and animals with experimental diabetes which baseline hydrostatic pressure is already elevated due to the presence of diabetes. This increase in glomerular hydrostatic pressure has been recognized as a major risk factor for the progression of kidney disease in experimental models of diabetes and could provide an explanation as to how nicotine accelerates kidney disease. We have recently performed a second set of experiments to determine what is the mechanism responsible for the increase in hydrostatic pressure during nicotine administration. These studies demonstrate that administration of an agent which blocks the effects of angiotensin II (a major kidney hormone) prevents the increase in glomerular pressure during nicotine administration. The beneficial effect of angiotensin II blockers were observed both in normal animals and animals with experimental diabetes.

The results of the present study provide very exciting information about the potential mechanism of nicotine induced renal damage. Most importantly, these results suggest that alterations in angiotensin II could be responsible for the changes in renal function induced by nicotine administration. Important implications of such a finding would be that the use of a commonly prescribed medication for the treatment of hypertension and proteinuria (angiotensin converting enzyme inhibitors and angiotensin II receptors antagonist) may prevent smoking/nicotine induced renal damage. Based on the limit success of smoking sensation treatments, the possibility that a rather benign medication could prevent or retard the effects of smoking/nicotine on renal function provides an extremely attractive alternative therapy.

B8

The acute effects of low dose naltrexone on ad lib smoking in normal heavy smoker and chippers

Olmstead, Richard E., Caskey, Nicholas H., Madsen, Damian C., Terrace Scott M., Iwamoto-Schaap, Paula N., Griffith, Tina M., Wirshing William C., Jarvik, Murray E.
University of Californa, Los Angeles, VAGLAHS-West LA

The potential of the opiate antagonist naltrexone as a pharmacotherapy for smoking cessation has been investigated with mixed results. This study investigates the acute effects of naltrexone on ad lib smoking. The twenty-nine subjects included heavy smokers (>15 cigarettes per day, n= 19) and chippers (< 6 per day, n= 10). In a double-blind, repeated measures design, subjects participated in three 12-hour sessions during which they were given either placebo, naltrexone 50 mg, or naltrexone 100 mg. Subjects were exposed to all three drug conditions in random order. Subjects smoked ad lib during the sessions. Dependent variables included: measures of smoking topography, questionnaire measures of urge to smoke, expired carbon monoxide, and serum cotinine and nicotine. Preliminary results indicated a main effect of dose which followed a quadratic pattern. Subjects smoked fewer cigarettes with 50 mg naltrexone than with placebo ($p <$ .005) but the 100 mg condition did not significantly differ from placebo. A significant main effect of group on interpuff interval was found where smokers showed significantly longer interpuff interval than chippers ($p <$ .001); a linear trend interaction for inter-puff interval was also suggested indicating a difference in dose response between the two groups ($p<.08$, $eta^2 = .15$). A significant main effect of group on puff duration was observed with smokers taking longer puffs than chippers ($p < .001$). Findings concerning self-report measures of urge to smoke will also be presented.

B9

Bupropion for smoking cessation: a randomized trial

Simon, Joel A .
University of California, San Francisco and the San Francisco VA Medical Center

Standard smoking cessation interventions include counseling, nicotine replacement therapy, and self-help literature. Because smokers are more likely to have a past history of depression and smoking cessation may increase symptoms of depression, the use of antidepressant medication for smoking cessation has been proposed as a possible aid for smoking cessation. A few studies have reported bupropion, an antidepressant, an effective adjunct for smoking cessation. However, the effectiveness of bupropion has been studied in only a few populations to date.

We are conducting a randomized blinded clinical trial at the San Francisco VA Medical Center in which smokers receive standard treatment that includes 2 months of the nicotine patch, counseling, and use of self-help literature. In addition, approximately 50% of participants are randomly assigned to receive 7 weeks of bupropion whereas the remaining 50% of participants are randomly assigned to receive an identical placebo. Neither the participants nor the investigators know who has been assigned to receive the active drug. If the addition of bupropion to standard therapy increases biochemically-confirmed smoking cessation rates at one year, it may become an important addition to smoking cessation programs targeted at diverse populations of heavily addicted smokers.

This study is currently following participants. A total of 244 current out-patient smokers, both veteran and non-veterans, have been enrolled and are being followed. Twelve-month follow-up data are available for 222 participants. By self-report, 60% of the participants (n = 113) have quit smoking at the end of treatment (8 weeks) and 41% of the participants (n = 91) have quit smoking at 6 months of follow-up. The self-reported end-of-treatment quit rates are 64% for the bupropion group and 56% for the placebo group (P = 0.20). The self-reported 6-month and 12-month quit rates are similar in both groups. The 12-month quit rates for these participants, validated by either saliva cotinine or proxy, are 18% in the bupropion group and 27% in the comparison group ($p = 0.09$) A total of 5 participants have died, 2 in the bupropion group and 3 in the comparison group.

If the current trend continues through the completion of follow-up, the addition of bupropion to nicotine replacement and counseling would not appear to further increase quit rates over that expected from nicotine replacement and counseling alone.

B10

Effectiveness of two different regimens in a smoking clinic

Sherman, Scott E.
University of California, Los Angeles

Several studies have been conducted on the efficacy of different smoking cessation therapies. However, few studies have looked at their effectiveness in everyday clinical practice. This study is an analysis of the effectiveness of bupropion versus bupropion plus nicotine patch in a routine clinical setting at the Sepulveda VA's Smoking Cessation Clinic (SCC). Our primary goals are to determine the completion rates of the SCC, six-month abstinence rates, and evaluate the differences in cost among each treatment regimen.

During the period of February 25, 2000 to June 29, 2001, all patients enrolled in the SCC were eligible to participate in the study. Consenting patients had the option of agreeing to one or more of the following study components: 1) random assignment to receive bupropion or bupropion plus nicotine patch, 2) complete the baseline and follow-up survey, and 3) give access to their medical records. The SCC received a total of 708 patient referrals. Of these, 388 (55%) attended at least one session of the eight-week long program and 274 (71%) consented to participate in one or more parts of the study. Of the 274 study patients, 112 were in the bupropion treatment group, 115 were in the combination group, 45 received nicotine patch alone, and 2 did not receive any pharmacologic assistance. Although the study did not randomly assign patients to nicotine patch treatment alone, patients who agreed to participate but had medical contraindications to the bupropion or combination treatment group were still included in the study.

Side effects were reported by 48% of people taking bupropion, 53% of people taking combination therapy, and 41% of people taking nicotine patch. The most commonly reported side effects were dry mouth (28%), insomnia (17%), and constipation (13%). Despite the large proportion of patients experiencing side effects, only 14% switched to a different regimen than was originally assigned. Treatment regimens were changed in 12% of patients that started on bupropion, 17% of patients that started on combination therapy, and 14% of patients that started on nicotine patch.

Two-month smoking abstinence was based upon patient self-report and verified by carbon monoxide testing. Among the 274 study patients, 30% successfully completed the 2-month program. 26% of people taking bupropion, 37% of people taking combination therapy, and 27% of people using only nicotine patch completed the SCC (p=0.08).

Six-month smoking abstinence rates are assessed using follow-up telephone interviews. At this time, 9% of patients who used bupropion, 13% of patients who used combination therapy, and 9% of patients who used nicotine patch alone remained non-smokers at six months. Six-month follow-up interviews will be conducted through December 2001.

These results indicate that there may be a significant difference between bupropion and the use of bupropion plus nicotine patch, both in terms of 2-month and 6-month abstinence rates. Significant differences in the cost of these medication options will also be important in setting up a standard plan to be used in a routine clinical setting that will be best at helping people quit smoking.

B11

Pager-cued therapeutic messages for smoking cessation: a pilot study

Carmody, Timothy P.
University of California, San Francisco

Veterans smoke at a higher rate than California's population at large. Many are long-term heavy smokers with multiple previous quit attempts who are highly motivated to try new tools to help them to quit. The overall purpose of this pilot study was to determine the feasibility, acceptability, adherence rates, and efficacy of pager-cued therapeutic messages, using alpha-numeric pagers, in a group of outpatient veterans attempting to quit smoking. Our goal was to develop and test the feasibility of using pager technology as an innovative smoking cessation intervention for special populations of smokers such as outpatient veterans. An additional aim is to improve access, affordability, and acceptability of existing smoking cessation treatments.

Enrolled participants were provided with alpha-numeric pagers after having first completed baseline questionnaires about their smoking history, smoking habits, attitudes about smoking and smoking cessation, and other related information. Participants then received brief counseling and instructions on use of the pagers and retrieval of messages. Pager-cued therapeutic messages designed to enhance motivation or readiness to quit, coping skills, problem-solving, and relapse prevention were then sent to participants for a period of three months. Some messages were applicable to all participants, while others were individually tailored to the specific needs and preferences of individuals. Participants then received follow-up telephone counseling at regular intervals (weekly for the first month, then monthly until 3 months) during the time they were receiving the pager-cued therapeutic messages. Outcome measures, such as smoking status, and adherence and helpfulness ratings, were obtained 6 months following enrollment.

Baseline data for the 44 enrolled participants showed an average age of 54.1 years, average pack year history of 53.0, and current average level of smoking at 26.2 cigarettes per day. Ethnic composition was as follows: 36.4% are African American, 2.3% are Asian, 52.3% are Caucasian, and 9.1% identify themselves as Other. Stated history of alcohol or drug abuse was prevalent at 67.4%, as was a history of depression (34.9%). The mean baseline score on the revised Fagerstrom Tolerance Questionnaire, used to measure degree of dependence on nicotine, was 4.3 out of a possible 7. At 3 months, 28 participants rated the pager-cued therapeutic messages as very helpful (mean helpfulness rating of 8.1 ± 1.8 on 10-point scale). At 6 months, 7 participants (33.3%) have reported abstinence from tobacco. Of the remaining two-thirds who continued to smoke, the mean number of cigarettes smoked per day was 14.1, or a 46.2% self-reported reduction over baseline cigarette use.

We are encouraged by the findings of this pilot study, particularly the aggregate participant satisfaction with the pager-cued messages and its impact on smoking reduction and cessation assessed at 3 and 6 months. The use of pager-cued therapeutic messages represents a merger between technology and behavior-change strategies designed to promote forward movement through the stages of change, maintenance of self-regulatory coping responses, and relapse prevention.

B12

Dissemination of a smoking cessation program for inpatients

Taylor, C. Barr
Stanford University

This project focuses on issues related to the implementation and dissemination of existing approaches to tobacco control. The goal of this project is to disseminate a scientifically-tested smoking cessation program (called Staying Free) for hospitalized patients to a wide range of hospitals in the south San Francisco Bay area.. We hope to demonstrate that the program will be equally successful when used in these hospitals as it was when implemented as part of rigorous studies.

In the first year of the study, the Staying Free program was implemented in six hospitals in the southern San Francisco Bay area peninsula. The hospitals involved include a Veterans Administration, county, University, managed care, small and large community. Each has adapted the original Staying Free model of implementation in order to capitalize on local hospital resources and issues. These models address systems for identifying smokers and for providing educational, counseling, pharmacological, and follow-up components. Intervention materials developed in partnership with the participating hospitals include a relaxation CD, posters for patients' rooms, training materials for staff, and interventions for Hispanic and Vietnamese populations. Over 300 professionals have been trained as part of the implementation program.

Three hundred twelve smokers (203 men; 109 women) received the program as part of the research in one of the six participating hospitals during the first phase of the trial. Participants were middle-aged ($M = 50.9$, $SD = 12.9$), and moderately diverse (66.6% Caucasian, 13.6% African American, 11.3% Latino, 4.3% Asian American, and 4.3% Other/Unknown). Initial data ($N = 175$) suggest that the program results in cessation rates of approximately 27.4% (22.4% to 33.3%) at six-month follow-up across hospital settings, with patients lost to follow-up counted as smokers. These results are comparable to controlled trials.

To provide the program, hospitals need an administrative commitment to providing smoking cessation services, funding for a part-time coordinator of the program, and an advisory board dedicated to developing a workable model of implementation. A key challenge to implementation is the current climate of limited resources in hospitals, including staffing shortages that make it difficult to meet acute care demands.

In the last phase of the project, we will determine if the participating hospitals are able to continue to successfully provide the program. However, based on preliminary evidence we believe that we have shown that an effective smoking cessation program for patients who smoked prior to hospitalization can be successfully implemented in any hospital setting. National systems such as NCQA, JCAHO, and the AMA need to set policies that encourage hospitals to prioritize the identification and treatment of smokers; and such services need to be reimbursed. Such policies would have a major impact in California and nationally on increasing smoking cessation rates.

B13

Similar expression pattern of alpha-conotoxin MII sites and the dopamine transporter in control and MPTP lesioned monkey basal ganglia

M. Quik[1*]; Y. Polonskaya[1]; J. Kulak[1]; J.M. McIntosh[2]
[1]The Parkinson's Institute, and [2]University of Utah

Parkinson's disease is a neurological disorder characterized by progressive degeneration of the nigrostriatal dopaminergic system that results in movement dysfunction. Accumulating evidence now suggests that nicotinic receptors may provide a therapeutic target for treatment. This includes the demonstration of an inverse relationship between smoking and the incidence of Parkinson's disease, and work showing that nicotine and nicotinic agonists may ameliorate parkinsonism in different animal models.

Previous studies from our laboratory have shown selective changes in expression of nicotinic receptor subunit mRNAs in squirrel monkey (*Saimiri sciureus*) substantia nigra after administration of the dopaminergic toxin MPTP. As well, we showed that there were declines in α-conotoxin MII sensitive nicotinic acetylcholine receptors, which may represent α3/α6 containing nicotinic receptors, after nigrostriatal damage in monkey basal ganglia. These findings suggest that these sites may be important in the nigrostriatal dopaminergic system. In the present study, we investigated the pattern of expression of ^{125}I-conotoxin MII binding and compared it to that of the dopamine transporter, a marker of dopaminergic neurons, both under normal conditions and after nigrostriatal degeneration. Similar expression patterns in normal and lesioned animals could suggest that these nicotinic receptor sites and the dopamine transporter share a similar cellular localization.

Our results show that there were mediolateral and dorsoventral gradients in the distribution of ^{125}I-conotoxinMII receptor sites in the striatum and substantia nigra in control brain, which closely paralleled those in the dopamine transporter as assessed using ^{125}I-RTI-121. Administration of MPTP, a neurotoxin that selectively destroys dopaminergic nigrostriatal neurons, led to decreases in ^{125}I-conotoxinMII sites in the basal ganglia that were most pronounced in the dorsal caudate, lateral putamen and ventrolateral substantia nigra. The selective regional vulnerability of the ^{125}I-conotoxinMII sites in monkey basal ganglia after MPTP treatment correlated very well with declines in the dopamine transporter in these same brain areas ($P < 0.001$). The present results show that the dopamine transporter and the CtxMII sensitive nicotinic receptor population (putative α3/α6 containing sites) are altered in a similar manner after nigrostriatal damage. These findings suggest that these nicotinic receptors are primarily localized to dopaminergic neurons in the basal ganglia.

The MPTP-lesioned nigrostriatal degeneration model for non-human primates causes changes in nicotinic receptors that are similar to those seen in Parkinson's disease patients. This work is therefore relevant to treatment of Parkinson's disease with nicotinic receptor ligands, particularly since smokers exhibit elevated levels of nicotinic receptors and are less likely to develop the disorder.

B14

a-Conotoxin MII sensitive nicotinic receptors are selectively decreased in the caudate-putamen of parkinsonian monkeys

[1]Quik, M. , [1]Kulak, J.M. and [2]McIntosh, J.M.
[1]The Parkinson's Institute and [2]University of Utah

Nicotinic receptors in the basal ganglia are a potential target for new therapeutics for Parkinson's disease. Epidemiological studies show that tobacco use is associated with a decreased incidence of Parkinson's disease, a neurodegenerative disorder associated with a loss of dopamine neurons in the substantia nigra. The agent in tobacco products responsible for the neuroprotective effect is not known. However, accumulating evidence indicates that nicotine has a neuroprotective role against nigrostriatal degeneration in rodents. Furthermore, results show that activation of nicotinic receptors causes dopamine release in this region. These observations raise the question whether the nicotine in tobacco products mediates the apparent neuroprotective effects of smoking observed in Parkinson's disease.

To determine which nicotinic acetylcholine receptor subtypes may be relevant for Parkinson's disease, we used [^{125}I]epibatidine, an agonist that labels nicotinic receptors containing α2-α6 subunits. Our results show that [^{125}I]epibatidine binding sites are expressed throughout control monkey brain, including the caudate-putamen and substantia nigra, areas of relevance to Parkinson's disease. As an approach to determine the nicotinic receptor subtypes that were involved, competition studies were done. For this purpose, we used the α3/α6-selective antagonist α-conotoxinMII as well as other nicotinic receptor subtype selective agents. α-conotoxinMII maximally inhibited 50% of [^{125}I]epibatidine binding in the caudate-putamen, but had no effect on binding in the frontal cortex or thalamus. In contrast, inhibition experiments with nicotine, cytisine, and A85380 showed that these agents resulted in a complete block of [^{125}I]epibatidine binding in all regions investigated, and did not discriminate between the α-conotoxinMII sensitive and insensitive populations in the striatum. Furthermore, experiments showed that nicotinic receptors expressed in the primate striatum have similar affinities for nicotine, cytisine, and A85380. These data thus indicate that α-conotoxin MII is the one ligand that discriminates between the different nicotinic receptors populations in the caudate and putamen.

To assess the effects of nigrostriatal damage, monkeys were rendered parkinsonian with the dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Animals with moderate striatal damage (dopamine transporter levels ~30% of control) had a 40-50% decrease in [^{125}I]epibatidine binding. Inhibition studies showed that the decrease in epibatidine binding was due to loss of α-conotoxin MII sensitive nAChRs. Monkeys with severe nigrostriatal damage (dopamine transporter levels ≤ 5% of control) exhibited a 55-60% decrease in [^{125}I]epibatidine binding, which appeared to be due to a complete loss of α-conotoxin MII nAChRs, and a partial loss of other nicotinic receptor subtypes.

The present data thus indicate that, in lesioned animals, α-conotoxin MII sensitive nicotinic receptors are selectively decreased after nigrostriatal damage. These results may have important implications for therapeutics with nicotinic receptor specific drugs for Parkinson's disease

B15

Mechanisms underlying regulation of respiratory pattern by nicotine in preBötzinger Complex

Shao, Xuesi M and Feldman, Jack L
University of California, Los Angeles

Smoking has been associated with some prevalent disorders of respiratory control such as sudden infant death syndrome (SIDS) and sleep-disordered breathing (sleep apnea). SIDS is the second-ranking cause of infant death between one month and one year of age. Impaired control of breathing and arousal responsiveness are believed to be the underlying mechanisms. The incidence of SIDS is known to correlate to maternal smoking, but how it causes SIDS is unknown. About 6 to 7 percent of the U. S. population have sleep apnea, i.e., frequent episodes of limited or no ventilation during sleep. The public health burden attributable to sleep apnea is substantial because sleep apnea can cause high blood pressure and other cardiovascular disease, memory problems and lack of sleep leading to job impairment and motor vehicle crashes. Nicotine from cigarette smoking acts on nicotinic acetylcholine receptors in the brain affecting respiratory pattern. The goal of this project is to understand the cellular and synaptic mechanisms underlying modulation of breathing by nicotine and to identify the pharmacology subtypes of nicotinic receptors mediating the effects. Insight into these cellular processes will provide a rational basis for prevention, diagnosis and treatment of SIDS, sleep apnea and respiratory failure during organophosphorus poisoning.

Respiratory rhythm is believed to be generated in the preBötzinger Complex (preBötC) in the brainstem in mammals. Using a medullary slice preparation from neonatal rat which contains preBötC, we examined the effects of nicotine on inspiratory neurons in preBötC and on the respiratory-related motor activity from hypoglossal nerve (XIIn). Microinjection of nicotine into preBötC increased respiratory frequency and deceased the amplitude of inspiratory bursts, whereas when injected into XII nucleus induced a tonic activity and an increase in amplitude but not in frequency of inspiratory bursts from XIIn. Bath application of nicotine (0.2-0.5mM, approximately the arterial blood nicotine concentration immediately after smoking a cigarette) increased respiratory frequency up to 280% of control in a concentration-dependent manner. Nicotine decreased the amplitude to 82% and increased the duration to 124% of XIIn inspiratory bursts. In voltage-clamped preBötC inspiratory neurons (including neurons with pacemaker properties), nicotine induced a tonic inward current of -19.4 ± 13.4 pA associated with an increase in baseline noise. Spontaneous excitatory postsynaptic currents (sEPSCs) present during the expiratory period increased in frequency to 176% and in amplitude to 117% of control values; the phasic inspiratory drive inward currents decreased in amplitude to 66% and in duration to 89% of control values. The effects of nicotine were blocked by mecamylamine (Meca). The inspiratory drive current and sEPSCs were completely eliminated by CNQX in the presence or absence of nicotine. In the presence of tetrodotoxin (TTX), low concentrations of nicotine did not induce any tonic current or any increase in baseline noise, nor affect the input resistance in inspiratory neurons. These effects could not be blocked by nicotinic antagonists α-bungarotoxin, methyllycaconitine (MLA), but were completely blocked by dihydro-β-erythroidine (DH-β-E), hexamethonium and partially blocked by tubocurarine. Bath application of RJR-2403, a nicotinic agonist selective for the α4β2 nicotinic receptor, or cytisine, an agonist selective for the β4 subunit containing nicotinic receptors, induced effects similar to those induced by nicotine. MLA had little effect on the RJR-2403 or cytisine induced changes in respiratory pattern and respiratory neurons, but DH-β-E completely blocked the RJR-2403 or cytosine induced effects.

In this study, we demonstrated that nicotine increased respiratory frequency and regulated respiratory pattern by modulating the excitatory neurotransmission in preBötC. Activation of nicotinic acetylcholine receptors (nAChRs) enhanced the tonic excitatory synaptic input to inspiratory neurons including pacemaker neurons and at the same time, inhibited the phasic excitatory coupling between these neurons. These mechanisms may account for the cholinergic regulation of respiratory frequency and pattern. Our results suggest that neither α7 nor α9 subunit homomers are involved in the modulatory actions of nicotine on preBötC inspiratory neurons and on respiratory pattern. The effects are likely mediated by the α4β2 nicotinic receptor. The β4 subunits may be also involved.

C1

Vapor-Phase Organics in ETS: Dynamics and Exposure

Singer, Brett C., Nazaroff, William W. and Hodgson, Alfred T. (P.I.)
Lawrence Berkeley National Laboratory

Environmental tobacco smoke (ETS) is the complex mixture of chemical vapors and particles to which non-smokers are exposed when in a room or house with smokers. ETS exposure is associated with increased risk of lung cancer, heart disease, and childhood asthma, but great uncertainty remains about which ETS components are most responsible for adverse health effects. Much is known about exposures to ETS particles and nicotine, but less is known about exposure to many individual organic vapors, including regulated toxic compounds. The relative and absolute room air concentrations of individual ETS vapors are influenced by smoking frequency, ventilation, and the tendency of some less volatile gases to stick (sorb) to indoor surfaces. Sorbing compounds are selectively removed from the air during smoking – thus reducing exposure – but can later desorb from surfaces, resulting in exposure long after active smoking has ceased. Significant exposure to ETS vapors can also occur if non-smokers enter a room shortly after smoking has occurred.

The overall objective of this project is to develop better methods and estimates of exposure to ETS organic vapors under realistic home conditions, taking into account the effects of sorption processes. We first conducted a series of experiments to quantify exposure-relevant emission rates of 28 organic vapor ETS components under a wide range of smoking, ventilation, and furnishing levels. These emission rates include sorption losses and can be used with indoor environment models and information on smoking frequency to predict exposures. Results indicate that sorption onto common indoor surfaces, such as wallboard and carpet, is an important removal mechanism for vapors identified by the State of California as Toxic Air Contaminants (TACs), including phenol, cresols and naphthalene. We have used the results of these experiments to develop an improved methodology for estimating exposures to ETS toxic components based on measured exposure to the tobacco-specific "tracer" compounds 3-ethenylpyridine (3-EP) and nicotine. A second series of experiments aims to quantify the effect, on exposure, of long-term sorption and re-emission of semi-volatile ETS components. This framework includes several weeks of daily smoking in a furnished 50-m^3 (12' x 12' x 8') chamber. Pollutant concentrations are being measured during 4-hr smoking, 10-hr post-smoking, and 10-hr "background" periods, to quantify exposures to toxic and other organic vapors relevant to individuals with varying occupancy patterns. We also will use the results of these experiments to investigate potential predictive models of longer-term sorption and re-emission in typical indoor settings.

This work provides important new information and methods to assess exposures to regulated toxic vapor components of ETS, both from direct tobacco smoke emissions and from the re-emission of compounds that sorb to indoor surfaces. Our results will help toxicologists focus on the most important disease-causing agents in ETS and provide guidance for epidemiologists to better assess ETS exposure based on household smoking rates, building ventilation rates and occupancy patterns.

C2

Evaluation of smoking room performance: laboratory experiments

Fisk, William J.[1], Wagner, J. [2], Sullivan, D. [1], Faulkner, D.[1], Alevantis, L. [2], Gundel, L. [1], Waldman, J.[2]
[1] *Indoor Environment Department, Lawrence Berkeley National Laboratory, Berkeley, CA*
[2] *Environmental Health Laboratory, California Department of Health Services, Berkeley, CA*

The purpose of this study is to quantify the effect of various design and operating parameters on the rate of leakage of ETS from smoking rooms to adjacent non-smoking areas. California Labor Code (Section 6400-6413.5) requires that air from designated smoking areas be exhausted directly to the outside by an exhaust fan and not be recirculated to other parts of the building. However, additional guidance is needed on the designs and operational conditions that most effectively minimize leakage of environmental tobacco smoke (ETS) from smoking rooms to adjacent non-smoking areas.

Twenty-eight experiments were conducted in a simulated smoking room with a smoking machine and an automatic door opener. Measurements were made of air flows, pressures, temperatures, three particle-phase ETS tracers, two gas-phase ETS tracers, and sulfur hexafluoride. The latter was released in the smoking room in a manner that simulated ETS generation. Analysis of the laboratory results has resulted in quantification of the various types of leakage flows, the effect of these leaks on smoking room performance and non-smoker exposure, and the relative importance of each leakage mechanism.

The results indicate that the first priority for an effective smoking room is to maintain it depressurized with respect to adjoining non-smoking areas. Another important ETS leakage mechanism to the non-smoking area is the pumping action of the smoking room door whenever it opens and closes, which transfers approximately 0.75 m^3 of ETS-laden air per door cycle to the non-smoking area. Substituting a sliding door for a standard swing-type door reduced this source of ETS leakage significantly. A "no door" configuration resulted in only modest non-smoker protection. Smoking room exhaust efficiencies in these experiments ranged from 0-94%, depending on operating conditions. ETS concentrations in the non-smoking area were reduced by a factor of 1.2 – 98, relative to the case where smoking occurs directly in this area. Measured results correlated well with results modeled with mass-balance equations (R^2 = 0.82-0.99).

This study is part of a larger research project whose objective is to investigate how smoking rooms with various design and operating parameters affect the ETS exposures of non-smokers in adjoining offices. The final phase of the study will evaluate the performance of smoking rooms located within actual buildings and also test our ability to predict smoking room performance using the model developed based on the data from our laboratory studies. The results of this project can be used by policy makers, engineers, and architects in future standards and guidelines on the design and operation of designated smoking rooms. The anticipated benefits are a reduction in the exposures of non-smoking workers to ETS leaking from poorly designed or operated smoking rooms.

D1

CT imaging to assist diagnosis of solitary pulmonary nodules

McNitt-Gray, Michael F.
University of California, Los Angeles

When imaging for lung cancer, x-ray CT scanning is often used, either as an initial scan or as a follow-up to another procedure such as a chest x-ray. The CT imaging exam often discovers solitary pulmonary nodules (SPNs). These usually appear as a small, roughly circular object in the lungs (sometimes referred to as a spot on the lungs). However, solitary nodules are not always cancerous. They have many causes including primary lung cancers, metastases from cancers at other primary sites and benign (non-cancerous) lesions that include benign tumors, infections, etc. Furthermore, cancerous and non-cancerous nodules are almost equally likely. In different studies, estimates range from 40-90% of all SPNs observed on CT to be benign. Unfortunately, there are few agreed upon image findings to distinguish benign from malignant nodules; the only nodules that are called benign with any degree of confidence are those with specific patterns of calcifications.

The goal of this research is the accurate diagnosis of lung cancers using imaging and computer analysis techniques. If the differences between cancerous and non-cancerous SPNs can be determined accurately, then more invasive and more expensive tests can be avoided.

The specific aim of this project is to collect the necessary data so that image processing and computer analyses can take place, which are being funded from another project. The data that is necessary to be collected is: patient image data and patient medical record data. Once we have these data, then we can apply our image processing tools to see if we can accurately predict the medical diagnosis based on the parameters extracted from the image data (such as the nodule shape, size, density and texture. We are now in the process of establishing the medical diagnosis (through medical record documentation) as well as radiological truth for all of these cases. From our data collection efforts, we may have 90 patients who have had at least one single image for us to analyze (on which we will perform two dimensional analysis) and another 60 patients who have had a volumetric imaging protocol performed with an intravenous contrast injection (for analyses on the three dimensional size and shape as well as information about contrast enhancement which has been shown to relate to nodule vascularity).

Future directions for this project are to continue and extend the data collection and diagnosis confirmation efforts so that we can begin thorough analyses in year 2. These will involve application of computer analysis techniques (developed under other funded research projects) to this image data to see if certain characteristics of the nodule (size, shape, etc.) can be used to help determine whether the nodule is cancerous or not.

As lung cancer screening programs get under way, manufacturers and other medical imaging equipment manufacturers are keenly aware of the need to develop tools to discern benign from malignant nodules. We are investigating this approach to create an accurate and noninvasive test so that we can reduce the need for additional, more invasive tests when investigating lung cancer.

D2

Novel DNA vaccines for the treatment of lung cancer

[a]Niethammer, Andreas G., [a]BaYi, [a]Xiang , Rong , [a]Dolman, Carrie S., J. [a]Ruehlmann, Michael , [b]Primus, F. James and [a]Reisfeld, Ralph A.
[a] *The Scripps Research Institute*
[b] *Vanderbilt University Medical Centern*

An oral DNA vaccine against human carcinoembryonic antigen (CEA) prevents growth and dissemination of Lewis lung carcinoma in CEA-transgenic mice.

We tested the hypothesis that a CEA-based DNA vaccine could overcome peripheral T-cell tolerance toward this human tumor-self antigen, stably transduced into Lewis lung carcinoma cells in CEA transgenic mice. It was of particular interest to determine whether this vaccine could induce a T cell-mediated, tumor-protective immunity, sufficiently effective to eradicate not only subcutaneous tumor growth but also prevent dissemination of pulmonary metastases. Since we recently reported that boosts of IL2 specifically targeted to the tumor microenvironment by an antibody-IL2 fusion protein could markedly enhance the tumor-protective immunity induced by a DNA vaccine against colon carcinoma, we assessed whether this concept was also applicable in a lung carcinoma model and examined some of its mechanisms of action.

A DNA vaccine encoding human CEA indeed broke peripheral T-cell tolerance toward this tumor self-antigen expressed by Lewis lung carcinoma stably transduced with CEA in C57BL/6J mice transgenic for CEA. This vaccine, delivered by oral gavage with an attenuated strain of *Salmonella typhimurium* (SL7207), and boosted with an antibody-IL2 fusion protein, (huKS1/4-IL2) induced tumor-protective immunity mediated by MHC class I antigen-restricted $CD8^+$ T cells, resulting in eradication of subcutaneous tumors in 100% of mice and prevention of experimental pulmonary metastases in 75% of experimental animals. Both CTL and antigen-presenting dendritic cells were activated as indicated by a decisive increase in their respective activation markers CD2, CD25, CD28 as well as CD48 and CD80. The marked increase in expression of CD28 on T cells and the costimulatory CD80 molecule on dendritic cells observed is of considerable importance because the activation of naïve T cells requires two independent signals: a) the first signal through antigen recognition and binding of the peptide: MHC complex to the TCR; and b) the second signal provided by ligation of CD28 with CD80 and/or CD86 to initiate T cell responses and production of armed effector cells. The increase over controls in expression of the high affinity IL2 receptor a-chain CD25 indicates that T cell activation took place in secondary lymphoid tissues after vaccination and tumor cell challenge. In this regard, future work already started, will focus on DNA vaccines with built-in chemokines serving as chemoattractants for T-cells and dendritic cells to secondary lymphoid tissues with emphasis on eradication of established and disseminated lung carcinoma metastases.

It is anticipated that such novel and effective DNA vaccines will become useful for the treatment of metastatic lung cancer and thereby reduce the human and economic cost of tobacco use.

D3

Chemoradiosensitization of human lung cancer cells

Yang, Li-Xi
California Pacific Medical Center

The goal of this investigation is to develop a novel taxol analog, taxoltere pnip, as an effective chemoradiosensitizing agent for improved lung cancer therapy. Studies *in vitro* and *in vivo* showed that taxoltere pnip was remarkably more potent in chemoradiosensitizing H23 human non-small cell lung cancer cells than parent drug taxol. Moreover, taxoltere pnip was dramatically less toxic to normal tissues than taxol. The results of mechanism studies demonstrated that taxoltere pnip more efficiently induced apoptosis in H23 cells when combined with radiation, compared with drug alone or radiation alone or taxol plus radiation. The apoptotic effects of taxoltere pnip were closely correlated with its cytotoxicity on H23 cells. The key effector molecules (caspases-3/7) of apoptosis were activated by taxoltere pnip. Taxoltere pnip combined with radiation was significantly more effective in activation of caspases-3/7 than taxoltere pnip alone or radiation alone or taxol + radiation. The proteolytic cleavage of the substrate [poly(ADP-ribose) polymerase (PARP)] for caspases-3/7, was dramatically more efficient in cells treated with taxoltere pnip + radiation than with drug alone or radiation alone, taxol + radiation. The PARP cleavage was closely associated with activity of caspases-3/7 and apoptosis. In addition, phosphorylation of Bcl-2 protein was observed in cells treated with taxoltere pnip. When cells were treated with taxoltere pnip combined with radiation, the expression of bcl-2 decreased. Taken together, these studies strongly suggest that apoptosis could be the main mode of cell death caused by taxoltere pnip chemoradiosensitization. Caspases-3/7 and Bcl-2 could play important roles in apoptosis induced by taxoltere pnip or combination with radiation. We plan to further investigate the molecular events of apoptotic machinery that might account for striking chemoradiosensitization of taxoltere pnip. We will continue to accomplish the essential preclinical studies on taxoltere pnip. The results of these important studies will directly contribute to the development of this novel exciting chemoradiosensitizing agent for markedly improved treatment of lung cancer. If this project is successful, the benefits to lung cancer patients would be substantial.

D4

Activity of Irofulven in combination with other chemotherapeutic agents.

Kelner, Michael J. and McMorris, Trevor C.
University of California, San Diego

Illudins are natural products with a novel chemical structure isolated from the toxic Jack O' Lantern, a mushroom that grows throughout California. The mushroom received its unusual name because it glows in the dark in the fall. Under sponsorship of the TRDRP, our laboratory has been developing a novel chemotherapeutic agent, irofulven, which is derived from these Illudin toxins. Irofulven is currently being evaluated in a phase III (final) trial for pancreatic cancer. Based on promising initial results, the clinical trial has been awarded "fast track" status by the FDA. In addition, pilot or Phase II trials for pancreatic, ovarian, prostate, breast, and liver cancer have also been initiated.

All of these clinical trials are investigating the efficacy of irofulven as a single agent (monotherapy). However, most tumors are treated clinically with combination (multiple) drug therapy. To determine whether irofulven should be administered clinically in combination with other classes of drugs, we began systematically studying the interaction between irofulven and other agents.

Irofulven was evaluated in combination with 130+ conventional and experimental chemotherapeutic agents using both *in vitro* and xenograft models. Studies were designed to determine the drug-drug interaction (e.g. synergistic, additive, or antagonistic) that exists between irofulven and conventional agents. Drug-drug interaction was initially examined *in vitro* against MV522 lung cells. Agents deemed effective in these cell culture studies (combination index < 0.7) were then evaluated using the MRP-positive MV522 metastatic lung carcinoma xenograft. Our results indicate that taxanes (Taxol, Taxotere), topoisomerase I inhibitors (topotecan, irinotecan), aziridines (mitomycin C & thiotepa), and platinum-based agents all produced a statistically significant synergistic (supra-additive) antitumor effect (as measured by tumor remission rate or increased life span), when combined with irofulven against this MRP-positive drug resistant xenograft model. In several xenograft studies, the combination of irofulven and another conventional agent produced complete tumor regression (defined as no tumor regrowth in 6 months).

These findings suggest that future clinical studies against solid tumors should consider the combination of irofulven with one or more of these agents. Indeed, based on these studies, several human clinical trials have already been initiated to determine the efficacy of irofulven in combination with Taxotere® (docetaxel) and Camptosar® (irinotecan) against breast and lung cancer, respectively.

E1

Maternal DNA repair of tobacco-induced sperm lesions

Marchetti, Francesco , Coleman, Matthew, Mabery, Shalini and Wyrobek, Andrew J.
Lawrence Livermore National Laboratory

The purpose of this research is to identify and characterize the molecular and genetic factors in paternal germ cells and zygotes that can increase the risk for abnormal pregnancies in couples where the father smokes. We have selected the mouse as the model species because there is a high degree of similarity between mouse and human reproduction and development. We hypothesized that: (a) paternal exposure to tobacco smoke induces DNA lesions in sperm that accumulate during the repair-deficient period of spermatogenesis and are converted into chromosomal aberrations after fertilization; and (b) deficiencies in DNA repair genes of the female partner can increase the frequency of paternally transmitted chromosomal defects.

We investigated the induction of chromosomal aberrations at first metaphase after fertilization following chronic (three weeks) or acute exposure of male mice to diepoxybutane (DEB). The results showed that: chronic exposure to DEB resulted in a significant increase in the frequencies of aberrations of paternal origin at zygotic metaphases during the last week before mating only; exposure to 28 mg/kg DEB over seven days immediately before mating or as single exposure seven days before mating resulted in similar frequencies of chromosomal aberrations; daily exposure to 2 mg/kg DEB during the last week of spermatogenesis did not increase the frequencies of paternally transmitted chromosomal aberrations. Overall, these results show that the last week before fertilization is the critical time-window for the induction of chromosomal damage in sperm after exposure to DEB and that genetic lesions do accumulate in sperm.

To examine specific maternal DNA repair functions in the processing of DNA sperm damage, we determined the levels of gene transripts for *p53* (a cell cycle control gene), *XPA* and *XPC* (genes involved in the recognition of DNA adducts), *Ku86* and *Rad54* (genes involved in the repair of DNA double strand breaks), *XRCC1* (a gene involved in the repair of damaged DNA bases) and *Ape1* (a gene involved in the recognition of abasic sites) in unfertilized and fertilized eggs using RT-PCR. *RAD54* transcripts were consistently detected in both unfertilized and fertilized eggs, *XPA* and *XPC* transcripts were not detected, while all other genes were detected in one or the other cell type. The transcription profile of ~800 genes involved in DNA-repair related functions. Total RNA was isolated from oocytes free of contaminating cumulus cells and amplified by a new *in vitro* transcription process (RiboAmp™ RNA Amplification Kit, Arcturus). Approximately 470 genes, including *Cyclin A*, *Cenp B*, *Cdc2*, showed significant intensities above the confidence intervals for negative reference genes. The microarray findings confirmed the findings by RT-PCR and/or TaqMan.

This project represents an important step for understanding the molecular mechanisms linking paternal exposure to tobacco smoke, induction of genetic lesions in sperm, DNA repair capacity of the fertilized egg, and the risk of paternally transmitted chromosomal abnormalities. Work performed under the auspices of the U.S. DOE by the LLNL under contract W-7405-ENG-48.

E2

Effect of maternal smoking on human placental development

Genbacev, Olga and Fisher, Susan J.
University of California, San Francisco

During pregnancy the placenta functions as a lifeline for the baby, transferring oxygen and nutrients from the mother's blood while also removing wastes. Like other organs, the placenta (and consequently the developing baby) is vulnerable to the ill effects of toxic substances. The goal of this research project is to understand the effects of one such insult, maternal cigarette smoking, on placental development.

Unlike other human organs, normal placentas, without disease, are readily available for study. Thus, we already have a great deal of information about how this organ works. Placental cells invade about two inches into the uterus, a process that normally attaches both the placenta and the baby to the mother for the nine-month duration of pregnancy. Once this attachment is firmly in place, placental cells stop growing. Invasion also stops. Work from our group, funded by this program, shows that maternal cigarette smoking has severe negative effects on both placental growth and invasion.

We conducted experiments to understand the mechanisms by which smoking damages the placenta. Because we know that the placenta normally develops in a low-oxygen environment, we focused our studies on a molecule important in mediating the effects of low oxygen—the von Hippel-Lindau protein (pVHL). Loss of the expression of this protein causes patients to develop cancers, hence its classification as a tumor suppressor molecule. The absence of this protein in mice produces placental defects that are very much like those we find in the placentas of women who smoke. Taken together, this information suggested to us that the negative effects of maternal smoking on the placenta could be attributed, in part, to pVHL.

Research completed during the current year of funding used an experimental model of the human placenta so we could test this hypothesis in the laboratory. We exposed small pieces of placentas from women who do not smoke to the toxic chemicals found in the blood of cigarette smokers. Then we examined the effects of this treatment on levels of pVHL and other molecules involved in oxygen-mediated responses. We confirmed our hypothesis that these toxic chemicals alter expression of these molecules, and therefore fundamentally damage the placenta's ability to grow and invade. We are now studying a collection of placental tissues from women who smoked during pregnancy to determine if the same ill effects and molecular changes are seen in these tissues.

Our ultimate goal is to help women to stop smoking before and during pregnancy, a good point at which to begin the long process of permanent cessation. We already know that women who smoke cigarettes have a much harder time getting pregnant than women who do not. Once they do get pregnant, smoking harms the growth of the baby inside the uterus by damaging the placenta. Our works explains why smoking harms the placenta and in turn growth of the baby. This information could be presented as a component of educational programs that help women stop smoking before, during and after pregnancy.

E3

Identification of chemicals in cigarette smoke that inhibit growth, angiogenesis and oviductal functioning in picomolar doses

Talbot, Prudence
University of California, Riverside

We have previously shown that mainstream and sidestream cigarette smoke solutions contain chemicals that inhibit various processes including growth of tissue, angiogenesis, and oviductal functioning. Growth and angiogenesis were assayed using the chick chorioallantoic membrane (CAM) and oviductal functioning was assayed using in vitro explants of the infundibulum from hamster oviducts. The purpose of this study was to identify the chemicals in smoke solutions that produce these effects in the CAM and oviductal assays. Mainstream or sidestream smoke solutions were first concentrated and partially purified using solid phase extraction cartridges. Cartridge eluents that retained >90% of the inhibitory activity in our assays for growth, angiogenesis and oviductal functioning were subjected to gas chromatography and mass spectrometry (GC-MS) to identify their major chemical constituents. Pyridine derivatives were found to represent the largest group of chemicals in the inhibitory eluents and were therefore studied further. Each pyridine derivative identified in smoke was purchased from a commercial source, and its purity was verified using GC-MS. Various doses (10^{-3} to 10^{-16}M) of each pyridine derivative were tested in our assays using methods described previously. Pyridine by itself was not a strong inhibitor in any assay. However, single ethyl and single methyl substituted pyridines produced very strong inhibitory or adverse effects in the CAM assay on growth, vascular area, blood vessel pattern, and capillary plexus formation, and in the oviductal assay on ciliary beat frequency, oocyte pick-up rate, and contraction of oviductal smooth muscle cells. In some assays, the substituted pyridines were inhibitory at doses 10 million times less than pyridine itself.

These results are of interest for several reasons. This study shows that several pyridine derivatives in cigarette smoke inhibit of a broad spectrum of cell processes at pico and nanomolar doses, and thereby identify this class of smoke constituents as dangerous. Since picomolar and nanomolar doses of single ethyl and single methyl substituted pyridines inhibited most parameters studied, these chemicals could cause a number of adverse effects in smokers and may explain why smokers have difficulty with wound healing which requires angiogenesis, fertility which requires proper functioning of the oviduct, and fetal weight which requires normal growth of fetal tissues. The observation that a broad spectrum of processes is affected by these compounds suggests they act either by multiple mechanisms or by interfering with a fundamental process important to many or all cells. Our observations take on further importance in that at least one of the compounds identified as inhibitory at picomolar doses is on both the FEMA GRAS (generally regarded as safe) list and the FDA EAFUS (everything added to food in the United States) list, and is an additive in tobacco, food, and cosmetic products.

F1

A dynamic model of smoking and healthcare Expenditures in CA

Max, Wendy B.
University of California, San Francisco

This study will develop a series of related models that permit us to understand the impact of smoking on healthcare costs as a dynamic process. It will take into account the intensity of smoking (packs per day), the length of time one smokes, quitting behavior, the years since quitting, and the impact of aging. Thus, the models will allow one to analyze the impact of changing smoking behavior over time. For example, studies that have appeared in the literature to date have reported that former smokers have greater healthcare expenditures than current smokers. Dynamic models will allow us to show that while quitters often have the poorest health of all smokers at the time of quitting, their health nonetheless improves over time after quitting, and their expenditures are diminished. Separate models will be developed to analyze the impact of smoking on health, smoking-caused diseases, healthcare expenditures, and mortality. The models will be developed using national surveys, and will be applied to California to estimate the annual and lifetime healthcare expenditures that can be attributed to smoking in the state. The models will then be used to address a question of great policy relevance in California: what has been net effect of the California Tobacco Control program on the health of its citizens and healthcare costs?

To date, work has focused on the theory and estimation of models of smoking behavior and its impact on health. Theoretical models have been developed, datasets have been identified, and empirical estimation has begun. The estimation of the dynamic models involves multiple steps in an iterative process. Starting values for the process have been derived, and the final estimation of these models is in process. Preliminary results are encouraging. For example, for males the models indicate that longer duration of smoking is associated with poorer health, the more packs per day currently smoked the poorer the health status, the longer the time since quitting the better the health status, and that having ever smoked is associated with poorer health.

Future work will apply the dynamic smoking models to the impact of smoking on mortality. Models of the impact of smoking on nursing home expenditures in California will be estimated which include the institutionalization of sick smokers and also the institutionalization of people who live alone due to the loss of a spouse from smoking-related illness. Finally, the models will be combined to analyze the net impact of California's tobacco control programs. This will be accomplished by comparing the actual smoking behavior of the state's residents and resulting impact on healthcare expenditures with the results from a simulation of the status quo prior to 1989.

This study will provide a measure of the economic success of California's tobacco control programs in improving health and reducing healthcare expenditures in the state. How much money has the program saved the state? This knowledge will be valuable for charting future directions for the program and for other states that are considering implementing or altering their own tobacco control efforts.

F2

Cost-effectiveness of smoking cessation in patients with congestive heart failure

Lightwood, James M.
University of California, San Francisco

This grant investigates the economic and financial returns to smoking cessation therapy. This project estimates the cost effectiveness of smoking cessation in patients with congestive heart failure (CHF). The impact of smoking on prognosis of CHF patients has received little attention until recently. This study provides the first estimates of cost effectiveness (known to the investigators) of cessation in patients with CHF.

This study concerns patients who have developed CHF arising from left ventricular dysfunction, which is the principal form of heart failure caused by cigarette smoking. Recently published results from other researchers using the SOLVD clinical trial data has shown that smoking cessation is as effective in reducing mortality in patients with CHF as ACE-inhibitor therapy.

The cost and outcome of CHF was modeled over ten years from onset using a cohort time-varying Markov model analysis. The base case parameters used for the estimates are as follows. The relative risk (RR) for overall mortality was 1.38 (95% CI 1.14 - 1.68) in current smokers with CHF. The RR fell to approximately one (0.98, 95% CI 0.81 - 1.17) for all ex-smokers who had quit for least two years. The average annual mortality rate among all CHF patients was 0.125 and the reduction in risk was 0.15 with ACE-inhibitor therapy. The costs were CHF hospitalization: $6,750, annual cost of medication: $959, additional direct medical costs of a year of life with CHF: $15,170 in 1992 dollars. An intensive smoking cessation program with long term follow-up increased the permanent quit rate by 0.11 at a cost of $195 per smoker treated.

The cost-effectiveness (CE) ratio of smoking cessation incremental to ACE-inhibitor therapy is $5,883 per year of life gained from the provider perspective and $21,053 from the social perspective. The CE ratio of smoking cessation incremental to treatment with digoxen and diuretics is $4,891 from the provider prospective and $20,061 from the social perspective.

Future directions of research include a sensitivity analysis of results and extension of the model to smoking cessation in asymptomatic left ventricular dysfunction before the onset of CHF. Preliminary sensitivity analysis indicates that the results are not sensitive to reasonable variations in the parameters involving smoking cessation. For treatment of asymptomatic left ventricular dysfunction, ACE-inhibitor therapy and smoking cessation are cost saving over four years for the provider. For society, ACE-inhibitor therapy is cost saving, and smoking cessation has a CE ratio of $115 per year of life saved.

Over 2 million people have CHF in the US, costing over $14 billion annually. It is one of the most expensive conditions per patient, and is the 2nd largest cost for medical providers. The prevalence of CHF will grow significantly, and cost-effective and cost saving interventions are needed. This research indicates that smoking cessation in CHF patients extends life at a low cost both for the provider and society. Smoking cessation in patients with asymptomatic left ventricular dysfunction may be cost saving.

F3

Economic and financial analysis of smoking cessation in Adults 18 to 64 years old

Lightwood, James M.
University of California, San Francisco

This grant investigates the change in direct medical costs to the provider and society following smoking cessation in an individual. If smoking cessation is cost saving for society but not for the provider, the research will determine subsidies required for providers to deliver the therapies. Previous research has shown that smoking cessation is cost saving for an adult woman of age 18 to 44 years due to the reduction in costs from adverse reproductive effects of direct smoking and ETS exposure in children. The economics of smoking cessation in adult men remain an important policy issue.

The incidence rates of smoking related diseases and relative risk (RR) of each disease from direct smoking was used to estimate the excess risk due to current smoking. The decline in the RR of each disease was taken from the literature and used to estimate the reduction in excess risk following cessation. The expected cost savings were estimated by multiplying the expected cost of each incident (or where appropriate, prevalent) case times the reduction in excess risk, producing a time profile of savings following cessation. Where possible, the expected cost of the disease was adjusted for expected co-morbidity. The diseases included were heart attack, stroke, emphysema, Parkinson disease, ulcerative colitis, Crohn's disease, community-acquired pneumonia, and cancers of the bladder, oro-pharynx, larynx, esophagus, pancreas, and lung. A representative healthy man between 35 and 64 was modeled. Men over the age of 65 were removed from the simulation since they would enter Medicare. The present value of total direct medical costs saved for society following ten years of cessation are over $2,000 for a healthy man aged 35 to 64.

The current results are for continuous smokers. Preliminary estimates indicate the savings will be between $1000 and $1,250 after adjustment for expected future cessation in a typical smoker. Future work includes estimates for men between the ages of 18 and 34. The current estimates apply only to smokers who quit before the appearance of overt signs and symptoms of smoking related disease. Up to 40% of smokers do not quit before the onset of these symptoms. No research, to the investigator's knowledge, has adequately solved the problem of separating healthy and sick quitters. However, few smoking related diseases produce overt symptoms before the age of 35, therefore few younger men will be sick quitters. Estimates of savings for younger men should be applicable to most actual quitters between ages 18 and 35.

Smoking cessation produces cost savings in a healthy male continuous smoker aged 35 to 64, which are large enough to justify smoking cessation therapy. These estimates do not include cost savings or increased costs of added life in the elderly. However, they are essential for understanding the economics of smoking cessation. If the cost of extended life in the elderly outweigh the cost savings in adults, these estimates indicate that increased lifetime direct medical costs of smoking cessation can be significantly delayed by cessation in adult men.

F4

Did the 1999 $0.50/pack tobacco excise tax increase discourage adolescent smoking participation?

Gilpin, Elizabeth A.; Emery, Sherry; White, Martha M.; Pierce, John P.
University of California, San Diego

The goal of this research was to look for evidence that the voter initiated and approved $0.50/pack tobacco tax excise implemented in January 1999 discouraged adolescent smoking participation in California. Population-based, longitudinal telephone surveys of California adolescents conducted in cohorts who did not (early cohort: 1993-1996) and who did (later cohort: 1996-Fall 1999) experience the tax increase were compared with respect to smoking uptake and quitting rates during the respective 3-year follow-up periods.

Among 12-14 year old committed never smokers (adamantly deny they would smoke, n=1068), cigarette use by follow-up was 32.6% in the earlier cohort and 20.0% in the later one (n=734). In 15-17 year old committed never smokers, these transition rates were 34.7% (n=598) and 21.3% (n=377), respectively. In 12-14 year olds who already had experimented at baseline, transition to established smoking (report of smoking at least 100 cigarettes in lifetime) occurred in 32.5% (n=381) in the earlier cohort and 20.1% (n=374) in the later one. In 15-17 year olds, these rates were 38.1% (n=598) and 21.3% (n=377), respectively. Further, among 15-17 year old current (smoked in past 30 days) established smokers at baseline, in the earlier cohort (n=114), 13.6% were quit (no smoking in past 30 days) at follow-up, compared to 27.8% in the later cohort (n=145). In separate multivariate analyses of these transitions in the combined cohorts, adjusted for other significant influences on smoking (baseline demographics, having best friends who smoke, perceived peer anti-smoking norms, perceived compliance with school anti-smoking rules, perceived ease of access to cigarettes, exposure to anti-tobacco media and receptivity to tobacco advertising and promotions), cohort was significantly and independently related to the transitions in 12-14 year olds ($p<0.01$) and in 15-17 year olds ($p<0.05$).

If cohort is assumed to be a surrogate for the excise tax increase, our results suggest that the tax increase may have discouraged adolescent smoking participation in California. However, unmeasured environmental influences or marked changes in influences besides increased cigarette price during the later follow-up period could also have affected likelihood of transition. Nationally, adolescent smoking rates have increased markedly over the 1990s decade, although there is some evidence of a slight downturn by 1999 and 2000. The very low transition rates among California adolescents in the later cohort indicates that this generation of Californians will likely experience much less morbidity and mortality from smoking-related disease than their predecessors.

F5

Harm reduction through reduced tobacco exposure in continuing smokers

Gilpin, Elizabeth A.; Pierce John P.; White, Martha M.
University of California, San Diego

The goal of this research was to determine whether tobacco control strategies aimed at protecting nonsmokers from environmental tobacco smoke (ETS) and at fostering anti-smoking views in the general population might be influencing smokers to smoke less on a daily basis. Data were from the Tobacco-Use Supplement to the Current Population Surveys of 1992-93, 1995-96 and 1998-99. California (with its relatively long-standing Tobacco Control Program) was contrasted with the rest of the US.

Standardized daily smoking prevalence in California declined from 14.6% in 1992-93 to 13.9% in 1995-96 and to 12.4% in 1998-99. In the rest of the US, these rates were 18.8%, 18.3% and 16.7%. In 1999, only 5.3% of Californians with some college education smoked daily (6.9% in rest of US), levels comparable to those of US medical doctors in 1990. Previous national surveys from the mid 1970s to the mid 1980s, indicated that about 25-30% of US smokers smoked >25 cigarettes/day. In 1999, only 8.3% of all California smokers were heavy daily smokers (13.6% in rest of the US). In 1992-93, 16.3% of California smokers both worked and lived in smokefree environments, with this percentage increasing to 28.6% by 1998-99, but only 16.4% of smokers in the rest of the US were subject to both types of smoking restrictions in 1998-99, a rate similar to California's in 1992-93. In 1998-99, several questions assessed where smokers should be allowed to smoke; California smokers felt significantly more constrained than smokers in the rest of the US. In 1998-99, smokefree homes and workplaces and the perceived degree of constraint about where it is appropriate to smoke were all significantly and independently associated with lower daily cigarette consumption in a multivariate regression analysis adjusted for demographics and cigarette price.

These results suggest that smoking restrictions and social norms about the appropriateness of smoking may influence smokers' daily cigarette consumption. Because tobacco-related disease and mortality are known to be associated with the cumulative level of exposure to tobacco smoke (total pack-years), tobacco control measures aimed at nonsmokers (protection from ETS, promotion of anti-tobacco norms) should help reduce the harm from smoking to continuing smokers in the long-term.

F6

The effectiveness of tobacco prevention programs in California Schools

Rohrbach, Luanne
University of Southern California

California schools that receive Tobacco Use Prevention Education (TUPE) funds from the state's tobacco control program are required to design their program based on the Guidelines for School Health Programs to Prevention Tobacco Use and Addiction, published by the Centers for Disease Control and Prevention (1994). These guidelines specify the following: an anti-tobacco policy should be in place in the school, tobacco instruction should include information about psychosocial influences in addition to physiological consequences, prevention education should be especially intensive in the middle school years, program-specific teacher training should be provided, efforts should be made to involve parents, cessation supports should be available, and programs should be evaluated.

This paper examines the extent to which California schools have implemented the CDC guidelines, and whether implementation of the guidelines is associated with program outcomes. The study sample includes 65 middle and high schools statewide that were surveyed for the Independent Evaluation of the California Tobacco Control Program (1996-2001). Surveys of youth and classroom teachers were administered in 1996 and 1998. Teacher data provided information about implementation of the CDC guidelines for tobacco prevention programs. A composite score was created for each school, representing the degree of CDC guideline-based implementation. Program outcome indicators included students' use of cigarettes and smokeless tobacco, and tobacco use mediators such as beliefs about consequences of use, refusal self-efficacy, beliefs about norms, and tobacco-related knowledge. Changes in outcomes from 1996 to 1998 were regressed on program implementation scores. Preliminary results show that higher levels of implementation of the CDC guidelines predicted reductions in lifetime smokeless tobacco use and increases in tobacco refusal self-efficacy.

The results of this study have implications for school-based tobacco prevention in California and nationwide. According to the original CDC guidelines, all recommendations should be implemented to ensure the greatest impact. However, this study is consistent with previous studies showing that full implementation of the guidelines is rare. Our study results suggest that implementation is related to some program outcomes. Future studies should focus on linkages between program implementation data and outcomes.

F7

Evaluation of smoking room performance: survey results

Alevantis, L[1]., Liu, K-L[1]., Waldman, J[1]., Lucas, L[3]., Tsai, F[2]. and Flessel, P.[1]
[1] *California Department of Health Services*
[2] *California Environmental Protection Agency*
[3] *Public Health Institute*

The objective of the study reported here is to survey California workers in order to estimate the proportion of non-smoking workers employed in buildings with designated indoor smoking areas and who are potentially exposed to ETS leaking from these areas. The survey of California workers was accomplished by including questions about indoor smoking areas at the workplace in the existing series of the California Tobacco Surveys (CTS) funded by the California Department of Health Services (DHS). The CTS is a statewide, cross-sectional survey of smoking-related behavior. The study reported here is part of a larger research project whose primary objective is to investigate the effectiveness of the most important engineering design and operational parameters of smoking rooms that affect exposures of occupants of adjoining offices to environmental tobacco smoke (ETS).

Progress to date includes: (a) receipt and preliminary evaluation of response data from the 1999 CTS about indoor smoking areas at the workplace; and (b) completion of telephone interviews with all California local tobacco control jurisdictions (N=62) to establish a database of local ordinances relating to operation of smoking rooms.

The 1999 CTS consisted of a detailed long telephone survey of 14,729 subjects. Given that the 1999 annual average employment for California was 15,731,700, we found that 55% of the respondents to the CTS (which translates to 8,652,435 for the state's workforce) responded that they work in an indoor setting. 7% (or 605,670 of the state's workforce) work in buildings that are not smoke free, of which 24% or 145,361 work in buildings where smoking is allowed in a special smoking room or lounge. Therefore, we estimate that about 1% of the California workforce potentially may be exposed to ETS leaking from these rooms.

In order to properly evaluate the above data, we needed information from all the 62 local tobacco control jurisdictions in California regarding their ordinances for the operation of smoking rooms. Since a complete database with this information did not exist, our staff contacted via telephone all 62 jurisdictions. The results indicated that 29% (N=18) have ordinances prohibiting smoking anywhere at the workplace including smoking rooms, while the remainder do not have specific ordinances more strict than California Labor Code (Section 6400-6413.5) and, therefore, do not prohibit the operation of smoking rooms. Smoking jurisdictions interpreting broadly the aforementioned section of the California Labor Code are not included in these calculations.

Future activities include: (a) correction of the above estimates after proper weighting; (b) inclusion of the information we collected on local ordinances as an additional dimension in the data analysis; and (c) comparison of these estimates to those derived from the 2000 and 2001 California Adult Tobacco Survey (CATS) (the CATS are conducted once a year and include interviews of about 4,000 adults).

We anticipate that the results of this project can be used by policy makers to provide additional guidance on design and operation of designated smoking rooms and therefore, reduce unintentional exposure of non-smoking California workers to ETS leaking from poorly designed and/or operated smoking rooms.

F8

Long Beach restaurant and bar business data: no adverse economic effects related to the smokefree bars law

Lee, Julia A., Friis, Robert H., Ma, C., and Pervez, M.
California State University, Long Beach

Objective: We have been investigating the response from the City of Long Beach to the Smokefree Bars (SFB) Law (AB 13/3037), which extended protection from second-hand smoke in the workplace to workers in bars. Based upon recent census data, Long Beach, the fifth largest city in California, was designated the most ethnically diverse city in the nation. Among Long Beach residents, we found that approval for the SFB law increased from 66% to 73% between 1998-1999 and 2000-2001. On several measures we have found marked distinctions between restaurant-bars and stand-alone bars. For instance, attitudes toward the SFB law were more positive among owners/managers and workers in restaurant-bars than in stand-alone bars. Moreover, compliance with the SFB law was higher in restaurant-bars than in stand-alone bars. The purpose of this study was to analyze results that mirrored the economic status of the bar and restaurant business over time, in order to determine variations that could reflect direct effects of the SFB Law.

Methods: We collected business data specific to Long Beach from two sources: 1) the state Board of Equalization (BOE), which supplied sales and use tax information for each quarter from 1992 to 2000, and 2) the state Department of Alcoholic Beverage Control (ABC), which provided numbers of beverage-alcohol licenses once a year from 1990 to 2001. The sales and use tax information was compiled from businesses that served either food and no alcohol or food and alcohol. For comparative purposes, each of these BOE data points was viewed as a proportion of the total taxable sales. The ABC Department data included licenses for both restaurant-bars and stand-alone bars, as well as off-sale licenses for comparison.

Results: Among all sources of business data, there were no downward trends that could be linked to the Smokefree Bars Law. Within both types of business results, however, there was evidence of a 1995-1996 economic recession in Long Beach. Beginnings of an economic recovery, which appeared sooner for restaurants and bars that served beer and wine than for restaurants and bars that served beer, wine, and liquor, occurred from 1997 - 1999. Numbers of ABC licenses for stand-alone bars — whether serving beer and wine or beer, wine, and liquor — showed fairly steady decreases throughout the entire time period, with very little variation. Numbers of off-sale licenses, although higher than numbers of stand-alone bar licenses, also declined throughout the time period.

Discussion: These economic results from the City of Long Beach showed no adverse business effects associated with the SFB Law and are therefore consistent with previous investigations of tobacco-control policies and business effects. Interestingly, these economic data, like our other measures of response to the SFB law, showed notable differences between restaurant-bars and stand-alone bars. Further attention should be directed to stand-alone bars, in an effort to understand their unique situation and thereby provide appropriate assistance for implementation of the SFB law, which will expand the promotion of smoking cessation while reducing, smoking frequency, smoking uptake, and exposure to secondhand smoke.

F9

Evaluation of master settlement agreement implementation

Friis, Robert H.
California State University, Long Beach

The Master Settlement Agreement (MSA), signed on November 23, 1998, is an agreement among attorneys general representing 46 states, the District of Columbia, and the five US territories, and the major cigarette companies. The MSA provides for annual payments that total approximately $246 billion to be allocated among the 46 states, District of Columbia, and US territories. The MSA did not constrain the use of the funds nor proscribe their use for non health-related purposes. The opinions of the general public, health advocates, and national and local government officials appear to differ considerably regarding the use of the MSA funds. In order to determine the opinions of the general public, we conducted a telephone survey of a random sample of 1500 residents of the City of Long Beach, who were at least 18 years of age. Questions included alternative uses for MSA funds, as well as various uses within the category of health-related services. A total of 80% of respondents felt that the money should be used for improvement of health care services in comparison to other uses. Regarding various types of health-related programs, nearly 40% of respondents felt that funds should be used for keeping hospital emergency rooms open, while more than 20% agreed that the money should be used for anti-smoking education for youth.

F10

Courting scientists: are scientific integrity and public health compromised by tobacco industry affiliations?

Hong, Mi-Kyung, MPH; Bero, Lisa, PhD
University of California, San Francisco

The tobacco industry has had long-standing relations with the scientific community, the details of which have only recently become available through the Master Settlement Agreement of 1998. Documents located on the Philip Morris website chronicle intricate affiliations between the tobacco industry and prominent scientists and epidemiologists.

We are currently investigating case studies depicting the complex and often conflicting affiliations of scientists funded by the tobacco industry and health groups. Internal memos from Philip Morris show that researchers who are heavily dependent on the industry for their funding align themselves with the industry position that epidemiological studies and methods are not valid. Investigators who publish critiques of epidemiologic methods are seen by the tobacco industry as allies and are pursued for consulting purposes to further contention on these matters. Many scientists participated in the tobacco industry's campaign to refute data on adverse health effects resulting from exposure to environmental tobacco smoke. The documents candidly reveal industry tactics to recruit scientists to promote a public relations agenda regarding health effects and ETS. Internal memos describe the use of scientific consultants as potential ghost authors of industry-sponsored studies. Moreover, the documents show the receptiveness of scientists to support the tobacco industry's position regarding smoking and health effects.

Our research will heighten public awareness of the tobacco-sponsored funding streams behind research and how this may impact study conclusions. Financial disclosure of industry sponsorship of scientific studies is critical in order for policymakers and public health constituents to carry out balanced decisionmaking processes.

F11

How do African American young adults respond to issues raised by internal tobacco industry documents? A focus group study

Malone, Ruth E.
University of California, San Francisco

Tobacco is the #1 killer of African Americans, and African Americans also suffer disproportionately from chronic and preventable diseases directly related to smoking. Because such a disparity exists, it is imperative to expose strategies used by the tobacco industry to sustain its pervasive presence within African American communities. The tobacco industry has a long history of attempts to target their marketing, influence community leaders, and decrease or neutralize potential opposition from African Americans.

In this study, we search for and analyze internal tobacco industry documents to develop information briefs about how the industry views African Americans as political allies, as public relations opportunities, and as consumers. We present this information to focus groups of young adult (18-30 year old) African American Californians to assess their responses to different issues and gauge the potential usefulness of such information for countermarketing and other intervention purposes. We have selected this age group because they serve as role models for youth and because there is evidence that the industry is increasingly focusing its efforts toward them.

The tobacco industry has for many years carefully used its relationships within African American communities to push its policy goals and normalize tobacco presence. Problematizing this relationship requires making knowledge of the industry's behaviors more widespread and community-relevant. We will present preliminary analytic findings from the focus groups and discuss how tobacco control advocates might utilize similar information to shape tobacco control interventions at the community level.

F12

Advertising themes used to market cigarettes to African Americans

Burns, David M, MD; Anderson, Christy M; Reed, Mark B, PhD
University of California, San Diego

By the late 1970s, cigarette manufacturers were aware that certain cigarette brands, particularly those containing menthol, had become popular among African Americans. We investigated whether these manufacturers used different magazine advertising themes to market cigarette brands to African-American smokers.

We collected information on cigarette advertisements appearing in thirteen popular magazines circulated from 1980 to 1996. Among other information, we obtained the date and name of the magazine issue, the brand(s) of cigarettes advertised, and the themes depicted in the ads. The themes were put into four categories – people, health, economic, and other. The people themes typically represented descriptions of people or activities engaged in by people. The health themes encompass cigarette filters, health benefits, health concerns, and/or low tar/nicotine. The economic themes emphasize the cost of the cigarettes, marketing incentives, the length of the cigarettes, and/or the quantity of cigarettes. The other theme category includes themes that stress consumer-oriented issues (unrelated to economic issues), desribes visual aspects of the ad, or depict miscellaneous issues.

The analysis was restricted to the menthol cigarette brands popular among African Americans and the cigarette brands most popular among white smokers. Each theme category was compared within the brands popular among African Americans and the brands popular among whites. The advertisements that marketed brands smoked by African Americans was more likely to contain people themes and less likely to contain economic themes than those ads for brands popular among white smokers. There was no significant difference in the proportion of ads that carried health themes among brands smoked by African Americans and brands smoked by whites. Logistic regression modelling, which also controlled for the type of magazine in which the ad appeared and the frequency of issuance of the magazine, yielded similar results.

Future analysis will include the comparison of these same themes in magazines popular among African Americans.

F13

The temporal relationship between increases in low Tar cigarette advertising and increases in low tar cigarette sales

*Burns, David M., M.D., Reed, Mark B., Ph.D., Anderson, Christy M., B.S.
University of California, San Diego

During the 1950s the tobacco industry responded to research supporting a link between smoking and cancer by developing the filtered cigarette. In the 1960s, the filtered cigarette was followed by the introduction of cigarettes that delivered less tar as measured by the FTC method of machine cigarette smoking. From 1968 to 1999, the average sales weighted machine-measured tar decreased from 21.6 mg. to 12.0 mg. and the market share of low tar cigarettes increased from 2.5% to 86.6%. Because of the popularity and increasing market share of low tar cigarettes over time, we were interested in examining whether the advertising of low tar cigarettes drove low tar cigarette utilization. The purpose of this research was to examine the temporal relationship between the advertising and sales of low tar cigarettes and to demonstrate that increases in the advertising of low tar cigarettes preceded increases in the sales of these cigarettes.

For this study, cigarette sales data were obtained from the 1994 Maxwell report that summarizes annual cigarette sales from 1925 to 1990. Three research assistants reviewed cigarette advertisements from 13 of the highest circulating periodicals that accepted cigarette advertising from 1900 to 1996. The research assistants reviewed the advertisements and coded whether the ad displayed a low tar or low nicotine theme. We restricted the analysis of advertising to the top 20 cigarette brands with the most advertisements between 1967 and 1996. These brands represented 78% of all cigarette advertisements and 85% of all cigarette sales during this time period. The 20 brands were divided into 2 separate categories: low tar product extensions (low tar extensions from an existing brand family such as Marlboro) and free-standing low tar brands (new cigarette brands such as Vantage or Merit).

We analyzed the data by calculating the proportion of advertisements and sales for these 20 brands over time to determine the temporal relationship between advertising and sales. Our results showed that for both the low tar product extensions and the free standing low tar brands, increases in advertising for these brands preceded increases in sales. From these results we are now able to establish a temporal relationship between cigarette advertising and cigarette sales.

These results suggest that increases in low tar advertising drove increases in sales for low tar cigarettes. Because low tar cigarettes are viewed by many smokers as having lower risk, the advertising and availability of these cigarettes may have affected cessation efforts among smokers concerned with the health risks associated with smoking.

F14

Media and smoking among adolescent girls across ethnicity

Yang, Dongyun/Chou, Chih-Ping
University of Southern California

This project intends to study the relationship between media exposure and cigarette smoking behavior among African-American, Asian, Hispanic, and White female teenagers. The primary goal of the proposed study is to assess whether ethnicity will change the relationship and mechanisms of mass media influences on smoking behavior. Ethnic group differences on the effects of media exposure and other risk factors on smoking behavior will also be investigated.

White, African American, Hispanic, and Asian adolescent girls had different smoking behavior. White and Hispanic girls were at higher risk of smoking than African American and Asian girls. Smoking prevalence was increasing from 1990 to 1997 among White girls only, but no among other ethnic girls. Hispanic girls were more likely to be susceptible to smoking than other ethic girls. Advertisement of Camel increasingly influenced adolescent girls of different ethnic groups over time. Marlboro advertising also impacted adolescent girls. Newport seemed to be specifically popular among African American girls. White girls were slightly more likely to be exposed to tobacco industry promotional stuffs than other ethnic girls. Recognition of Marlboro, Camel, Virginia Slims, Newport, or other cigarette brand as advertised the most, favorite brand, or attracted attention the most had differential influences on future smoking possibility among different ethnic female teens. Among girls who never smoked a cigarette, even a few puffs and exposed to tobacco-related promotional activities, Hispanics and Asians were at higher risk of susceptibility to smoking than non-Hispanic Whites and African Americans. Exposure to cigarette advertising only increased risk of susceptibility to smoking among White and Hispanic girls, but not among Asian girls.

The findings were obtained using two California tobacco surveys among youth. Third data from the Independent Evaluation of the California Tobacco Control Prevention and Education Program will be included in the project to validate the findings. The next step is to focus on the mediational effects of smoking related attitudes, beliefs, or values on the relationship between media exposure and smoking behavior among adolescent girls. Interactions between exposure tobacco marketing and other risk factors (i.e., weight concerns, peer influence, acculturation) on smoking will be explored. Smoking behavior seemed to be different among adolescents from various ethnic groups. The media influences from tobacco marketing may play different roles in smoking behavior among adolescent girls across ethnicity. The project will provide more knowledge that will be helpful in designing effective tobacco prevention programs to reduce media influences on adolescent girls.

F15

Tests of the tobacco industry's youth smoking prevention ads

Henriksen, Lisa and Fortmann, Stephen P.
Stanford Center for Research in Disease Prevention

Public health advocates warn that the tobacco industry's recent foray into youth smoking prevention will backfire. In particular, ad campaigns by Philip Morris and Lorillard have been criticized for being more pro-industry than anti-smoking, and for using advertising strategies that are weak (at best) or counterproductive (at worst). Unfortunately, few empirical studies have tested the effects of these messages on youth. The goal of this research is to address concerns that the tobacco industry's smoking prevention ads will undermine California's tobacco control education efforts. Specifically, we hypothesize that exposure to the tobacco companies' smoking prevention ads: (a) improves students' impressions of the corporate sponsors and the industry they represent; (b) makes youth resistant to criticism of the tobacco industry (an inoculation effect), and (c) does more to encourage than discourage youth smoking (a boomerang effect).

Advertising exposure was manipulated under the guise of evaluating corporate advocacy advertising, which highlights a company's position on an issue rather than selling a particular product or service. Students (n=218) saw ads from Pfizer and Chevron followed by ads from Philip Morris about youth smoking prevention (Think. Don't Smoke); or ads from Philip Morris about charitable works (Working to Make a Difference); or ads from Anheuser-Busch about preventing underage drinking (the control group). Whether students know that Philip Morris is a tobacco company and their opinion of Philip Morris were measured before exposure. After exposure, students evaluated each commercial, and responded to questions about each corporate sponsor and the industry they represent.

The results suggest that youth smoking prevention ads sponsored by Philip Morris significantly improve the company's image. To this end, the ads work almost as well as those featuring Philip Morris' contributions to charitable causes such as aiding victims of domestic violence, sheltering homeless teens, and feeding the elderly. Students exposed to the smoking prevention ads also expressed more favorable opinions of the tobacco industry, although the difference between the control and treatment groups was not statistically significant.

Two additional experiments are planned. To test an inoculation effect, Study 2 will vary students' exposure to smoking prevention ads from tobacco companies and anti-industry ads from California's tobacco control education campaign. Images of specific tobacco companies, attitudes toward the tobacco industry, and support for tobacco control policies will be measured after exposure to one or both types of ads. The results from this study will determine whether exposure to the industry's smoking prevention ads reduce the impact of California's advertising. To test a boomerang effect, Study 3 will compare students' attitudes and intentions about smoking after seeing four anti-smoking ads from tobacco companies, or four anti-smoking ads from the California media campaign, or four drunk-driving ads (a control group). The results will demonstrate whether the tobacco industry's youth smoking prevention ads stimulate curiosity about smoking, promote beliefs that smoking leads to peer acceptance, or yield greater intentions to smoke. Ultimately, this research will inform policy efforts to regulate the industry's new advertising and to develop specialized counteradvertising to protect California's youth.

F16

Experimental evaluation of minors access to tobacco

Landrine, Hope, Ph.D.
San Diego State University

The purpose of this multi-stage study is to provide additional information about methods used by minors to obtain cigarettes illegally from stores, and to evaluate these methods in a systematic and controlled experimental design. Much of the data on illegal sales to children have been collected using methods that may differ significantly from the methods and procedures used by children when acquiring cigarettes for their own use. This study reports on the first phase of the investigation, where smoking youth were interviewed about the strategies they use to obtain cigarettes.

Equal numbers of boys and girls observed to be smoking cigarettes in public places (e.g., in shopping centers, at bus stops, in malls, near theatres) were approached by pairs of research assistants and asked if they would be willing to participate in a brief survey. Attempts were made to identify smoking children representing While, African American, Latino, and Asian ethnic groups. The survey consisted of 18 questions asking about smoking habits and strategies used to obtain cigarettes.

Preliminary analyses indicate that 41% of youth buy their own cigarettes, and 39.1% find it "easy" or "very easy" to buy. Of those youth who buy their own tobacco, 70% buy in liquor stores, and approximately 50% buy in convenience stores, small grocery stores, and gas stations. Approximately 40% of youth sometimes to always buy in their own neighborhood, in poor neighborhoods, pick small "trashy" stores to buy from, or buy where the clerk knows them. Few minors responded that they routinely lie about their age, say cigarettes are for someone else, bring fake notes from parents, buy cigarettes over the internet, or use fake ID to purchase cigarettes. Of the total sample (those that buy and don't buy their own cigarettes), 96% reported that someone gives them cigarettes, 34% steal cigarettes, 51% ask someone older to buy cigarettes for them, and 12.7 percent purchase cigarettes in Mexico (Tijuana).

One additional preliminary finding was that, while less than 4% of Caucasian, African American, or Asian American participants in the study report Mexico as a source of tobacco, 42% of Latino participants bought cigarettes across the border. The findings of the study will be discussed in terms of their implications for assessment methods used in federal and state access to tobacco studies, the validity of low access rates found in recent studies, and the continued need for primary prevention efforts aimed at reducing youth access to tobacco.

G1

Explaining racial differences in smoking

Landrine, Hope, Ph.D.
San Diego State University

The purpose of this project is to examine variables that might explain recalcitrant, Black-White disparities in smoking. In addition to investigating the well-known effect of socioeconomic status (SES), two unique variables were examined: racial discrimination and racial segregation. The specific aim was to assess the extent to which the latter two variables account for racial differences in smoking prevalence, quit rates, age of smoking initiation, stage of readiness to quit smoking, and degree of nicotine addiction.

This cross-sectional study entailed a survey mailed to a random sample of 4,000 Black and 2,000 White California adults ages 18 to 73 years who were residents of five specific Metropolitan Statistical Areas that differ in their degree of racial segregation. The survey return rate was 35% (N = 2,116). The impact of discrimination on smoking, as well as what appear to be ethnic differences in number, type, and the manner in which cigarettes are smoked are described. Similarly, the role of racial segregation in smoking rates and behaviors is also assessed, both for the sample as a whole and by ethnic group. These data are discussed in terms of their implications for smoking prevention and cessation programs culturally tailored for African Americans.

G2

Cultural / interpersonal values and smoking in a multicultural adolescent sample

Jennifer B. Unger, Ph.D., Sohaila Shakib, Ph.D., Anamara Ritt-Olson, M.A., Michele Moutappa, M.A., Peggy Gallaher, Ph.D., C. Anderson Johnson, Ph.D
University of Southern California

In a multicultural society, various traditional cultural values may influence adolescents' attitudes and beliefs, which in turn may influence their health risk behaviors. Cultural values that condone and celebrate adolescent individualism and rebelliousness might increase the risk of health risk behaviors such as smoking, whereas cultural values that encourage obedience to parents and authority figures might decrease the risk of adolescent smoking. Although some studies have assessed the role of cultural values in health behavior, none have measured cultural values among adolescents in a multicultural context and their associations with smoking behavior.

This study assessed the associations between cultural values and lifetime smoking in a multicultural sample of 2885 6th-grade adolescents in Southern California (mean age=11.3 years, 53% female, 43% Hispanic/Latino, 21% Asian/Pacific Islander, 10% White, 2% African-American, 17% Multi-ethnic, 7% Other, 9% ever-smokers). Scales were developed and pilot tested to measure values that are salient in many Hispanic and Asian cultures with high rates of immigration to California: Filial Piety, Saving Face/Simpatia, Respeto, Familism, and Machismo. A factor analysis revealed that the items clustered into a different, culture-independent factor structure: Respect for Adults, Traditional Gender Roles, Politeness, and Family Support. In a multivariate model, controlling for demographic characteristics and acculturation, Respect for Adults and Politeness were associated with a lower risk of lifetime smoking (Respect for Adults: highest tertile vs. lowest tertile Odds Ratio=0.21, 95% CI=0.13, 0.34, $p<.05$; Politeness: highest tertile vs. lowest tertile Odds Ratio=0.34, 95% CI=0.23,0.51, $p<.05$.) The strength of these associations with smoking did not vary significantly across racial/ethnic groups.

As adolescents interact with one another in a multicultural context, they might adopt the attitudes and values of their peers in addition to the values of their cultures of origin. Some of those values might be derivations of traditional cultural values from the multiple cultures that immigrate to the United States. In this way, values traditionally associated with particular cultures of origin may be adopted by adolescents of various ethnic groups, and those values might influence their decisions about health risk behaviors such as smoking. Encouragement of protective adolescent values may be an effective strategy for preventing problem behaviors such as smoking. Further research is needed to understand the structure of adolescent values and their associations with smoking behavior.

G3

Friendship patterns of adolescents by race/ethnicity

Hoffman, Beth and Johnson, Andy, PI.
University of Southern California

This study uses social network analysis to examine the friendship patterns of middle school students. As part of a larger survey, students at four schools in Southern California indicated their ethnicity and the names of three friends in their grade. It is hypothesized that students will be more likely to have friends of their ethnic group than friends of other ethnic groups. The friendship data was used to form a matrix of friendship patterns within the schools, and this data was analyzed using PROC IML in SAS to determine the proportion of each student's friends that were of each ethnicity.

Chi-square and logistic regression analyses indicate that the participants did exhibit patterns of association by ethnicity. As compared to mixed ethnicity participants, Asian participants were significantly less likely to have White friends, and over 5 times as likely to have Asian friends. Latino participants were more likely than mixed participants to have Latino friends, and "other" participants were more likely than mixed ethnicity participants to have "other" friends.

There are differences in friendship patterns by school as well, some of which seem to be related to the ethnic composition of the school sample. Participants at a school where 34% of the participants were White were more likely to have White friends than at the comparison school, where approximately 9% of the sample was White. However, participants at three schools were all less likely to have Asian friends than were participants at the comparison school, even though the proportion of Asians in the samples of the comparison school and one of the other schools was virtually identical.

Since rates of smoking vary by ethnicity, these findings have implications for determining the role of peer influence on adolescent smoking and planning effective prevention programs. As friendship patterns vary by school, patterns of social influence to smoke may vary as well. Future programs may wish to tailor the intervention to the social climate of the school for maximum efficacy

G4

Ethnic variation in the influence of family context variables on tobacco use among Asian, Latino, and Non-Hispanic White adolescents

Mouttapa, Michele, MA, Shakib, Sohaila, PhD, Ritt-Olson, Anamara, MA, Gallaher, Peggy, PhD, Trinidad, Dennis MPH, Johnson, C. Anderson, PhD, and Unger, Jennifer, PhD
University of Southern California

The family has a strong socializing influence on adolescent smoking. Studies generally show factors embedded within the family context are associated with adolescent smoking. Relative to this work, there has been a dearth of research that has examined whether family influences vary by ethnicity.

The purpose of this study is to examine whether ethnic differences in associations among family influence variables and smoking existed. Using an ethnically diverse sample of healthy 6th graders (n=2717; 52.6% female, 47.4% male; mean age= 11.3) in Southern California, this study used a self-administered survey to examine variation in lifetime smoking according to: (1) parental smoking (both, one, or either parents smoke), (2) parental monitoring (5 items; i.e., "Do you ever go to places that your parents don't want you to go," (3) parental attachment, (5 items; i.e., How often do you talk to your parents about what's on your mind," and (4) family structure (single parent family vs. two-parent family and stepfamily). Controlling for the effects of socioeconomic status, age, gender, and acculturation, separate odds ratios were calculated and compared for Asian, Latino, and Non-Hispanic White adolescents.

Logistic regression results revealed that high parental monitoring was a protective factor against smoking among Latino and Non-Hispanic White adolescents, but not Asian adolescents. High attachment to parents, low parental smoking, and living with both parents were associated with lower rates of smoking among Latino adolescents only. Asian adolescents had lower rates of ever smoking (4.4%) than Latino adolescents (10.7%), but did not differ significantly from Non-Hispanic White adolescents (6.9%). The findings suggest that across ethnic group identification, high parental monitoring is a key preventive measure against the initiation of adolescent smoking for all groups except for Asian adolescents. The findings suggest that the family may be an influential context for smoking prevention efforts. Ethnic differences in parental monitoring and attachment to parents should be considered in future health-related interventions.

G5

Smoking in Asian youth: effect of self-image and family

Weiss, Jie Wu
Alliant University

Objectives: The goal of this project is to examine how self-image affects smoking behaviors among Asian-American adolescents, mediated by acculturation and family functioning. Asian-American youth, especially recent immigrants, may be at risk for smoking initiation because their self-images may be challenged by multiple stressors, such as cultural adjustment, poor school achievement due to language barriers, changes in family structure, and lack of social connections in the U.S., in addition to the normal developmental issues of adolescence. The specific aims of the project are: a) to elucidate unique factors shaping cigarette smoking among Asian-American adolescents, such as interactions among self-image, acculturation, and family functioning; b) to examine similarities and differences in culture and family functioning and their impact on the relationship between self-image and smoking behaviors among four subgroups of Asian-American adolescents (Chinese, Filipino, Korean, and Vietnamese); and c) to examine how smoking may differ by gender in relation to acculturation, family functioning, and self-image.

***Progress*:** To date, we have achieved four major objectives essential to the project's timely progress. First, we identified schools with high densities of the Asian-American subgroups under consideration. Within Los Angeles County, these particular ethnic groups tend to live in clusters. Residential association occurs for various pragmatic reasons, such as speaking a familiar language in the neighborhood, finding traditional foods, sharing similar cultural customs, and recruitment by friends and relatives. Not only is it more efficient to recruit the targeted participants in these particular neighborhoods, but also participants recruited there may have closer ties to their culture and therefore be more representative. Because access to student participants is controlled indirectly, we next elicited cooperation from educational administrators. Once the administration supported the project, teachers were cooperative. The third objective was to pilot test our instruments and to translate the parental consent forms and the survey questionnaires into Chinese and Vietnamese for those new immigrants whose English proficiency may be limited. Our fourth achievement was data collection. Our target number was 200 students from each of the four designated subgroups. So far, more than 95% of the needed data have been collected. We have completed surveys from 2,736 students, including 351 Chinese, 245 Filipino, 236 Vietnamese, 126 Korean students, as well as 1778 students from other ethnic groups.

***Future Goals*:** Data entry is underway, to be followed by data analysis including chi-square tests, linear and logistic regressions, and structural equation model. We are going to report on the results of 2,610 questionnaires across four subgroups of Asian-American adolescents as well as four larger ethnic groups, (Asian, Black, Latino, and White students) to examine the similarities and differences in their smoking attitudes and behaviors.

***Study Implications*:** This is one of the first studies examining subgroups of Asian-American adolescents about smoking issues. Thus, the findings of the study will enhance understanding of the complex issues governing tobacco use among various ethnic groups. It will also permit the construction of more culturally appropriate and effective tobacco prevention programs specifically tailored to the diverse population of California.

G6

Tobacco use and acculturation: CA residents of Korean Descent

Hofstetter, Richard C.
Center for Behavioral Epidemiology and Community Health

Little research on the Korean population has been conducted in public health fields in spite of Korean's growing presence in California. Most studies do not differentiate between different subgroups of Asian and Pacific Islanders, in part due to insufficient sample sizes.

The purpose of this study is to examine the smoking prevalence rate, as well as other social and cultural determinants of smoking by focusing on the Korean population specifically.

A sample of 2500 adults and 625 adolescents of California residents of Korean descent will be interviewed by phone for approximately 30 minutes. Up to now, about 562 adults have been interviewed. First, a list of Korean surnames was developed using published sources and scanned into machine-readable form. Second, a subset of all telephone subscribers with Korean surnames was selected from all listed telephone subscribers in California. Third, the Korean subset of listings was randomly sampled and people of different ethnicity were screened out from initial calls. Questions on smoking uptake and cessation, family history of smoking-related diseases, level of acculturation, levels of family satisfaction, exercise, diet, etc. were asked.

Preliminary results (N =600 of 2500 projected) suggest that:

1) 15 % of all adults who are CA residents of Korean descent are current smokers. 36 % male adults and 4 % of female adults are current smokers.

2) 85 % of current smokers have tried to quit smoking: 86 % of male and 82 % of female adults have attempted to quit.

3) Level of acculturation plays a different role among men and women in their smoking prevalence. For men, the more acculturated they are to American culture, the higher their smoking rate. On the contrary, the less acculturated women are to American culture, the higher their smoking rate.

4) 61% of respondents answered that no one is allowed to smoke in the house. 23% answered that people are allowed to smoke in certain areas of homes.

More data analysis will be implemented before the AIM 2001 conference on the detailed smoking prevalence rate of adults by age, gender and their quitting attempts, family history of tobacco-related diseases, etc.

This study conforms that level of acculturation plays a role in smoking prevalence rate on Korean population in California and there are other social and cultural factors that affect smoking behaviors of California residents of Korean descent. Findings from this study will inform possible interventions for prevention and treatment by identifying social and cultural determinants of tobacco use specific to CA residents of Korean descent.

G7

Comparisons of Spanish language and English language participants of an internet self-administered smoking cessation study

Jacqueline L. Stoddard, Ph.D.,* Ricardo F. Muñoz, Ph.D., Kevin L. Delucchi Ph.D., Leslie L. Lenert, M.D., Eliseo Pérez-Stable, M.D., and Carlos Penilla, M.A.
University of California, San Francisco

Although there is mounting evidence that Internet administered programs for behavior change and smoking cessation are feasible and useful among English language web users, little is known about the feasibility of this technology among the Spanish language population. To address this need, the current project aims to continue development and evaluation of an extensible California State web-based resource for smoking cessation and to further demonstrate the feasibility of conducting smoking cessation research on the World Wide Web in Spanish and English. As a first step toward this end, we pilot tested the first of two conditions to be delivered in both Spanish land English. We compared data collected from two groups of smokers who participated in a self-administered Internet smoking cessation study: 1519 English language and 788 Spanish language subjects enrolled in equivalent versions of the same study, one in English, one in Spanish.

Both groups were similar in their use and evaluations of the site as well as smoking history (i.e., age at 1st cigarette, age 1st smoked regularly). However, the samples differed somewhat in demographics and smoking behavior. The Spanish language sample tended to be younger, more educated, more frequently employed, and had a higher proportion of male participants than the English sample. The Spanish sample also had the higher rate of individuals who met criteria for current major depression, who were exposed to smoking from others, and the lowest rate of individuals motivated to quit smoking, and who had used cessation aids to quit smoking. At six-month follow-up, 7-day abstinence rates were about 5% lower in the Spanish group (15.5%) than the English group (21.2%).

It is feasible to disseminate Internet-administered assistance for smoking cessation to both Spanish language and English language smokers. Demographic characteristics of the Spanish sample are similar to those of the early, English language, web users. Differences in abstinence rates between these two groups may be due to demographic factors rather than differing acceptance levels of this medium as form of help for smoking cessation. As more Spanish language individuals begin using the web for help with smoking cessation, the differences that we observed between the English and Spanish language sample may narrow and smoking quit rates in Spanish language participants may increase. Once fully developed, this site can be easily adapted for use in other settings with negligible cost associated with each additional volunteer, thus providing a potentially highly cost-effective treatment for smoking cessation.

G8

Feasibility and validity of hair collection from Latino children to assess exposure to environmental tobacco smoke

Conway, Terry L., Woodruff, Susan I., Edwards, Christine C.
San Diego State University

It is well established that environmental tobacco smoke (ETS) is a threat to the health of nonsmokers, particularly children. Current estimates suggest that Latino children are regularly exposed to ETS, probably in part due to conditions associated with being low-income. Many studies of ETS exposure among children rely on parent questionnaire measures that probably underestimate the exposure. There is a need for biochemical indicators that can provide accurate data on ETS exposure among Latino children, and that can validate parents' subjective reports of such exposure. While saliva and urine cotinine often serve as good biological measures, the intrusive nature of collecting these calls into question their acceptability within the Latino culture. Recently, hair analysis has become increasingly popular as a relatively non-intrusive health research tool to study ETS exposure, although the acceptability and ease of collection within Latino families is not known. Further, in this population, the correlation between parent-reports and children's exposure based on hair analysis has not been studied. The purpose of this study was to assess the feasibility of collecting hair from Latino children to measure ETS exposure, and to examine the concurrent validity between children's nicotine and cotinine in hair in relation to adult reports of children's exposure.

Spanish-speaking Latino adults (n=143) and their children were recruited by trained Latina lay community health advisors. Bilingual/bicultural measurement technicians collected two types of data: (a) adult's paper-and-pencil reports about the child's past-month exposure to cigarettes in the home and car, and (b) child's hair sample analyzed for nicotine and cotinine.

8.5% of those eligible declined to participate because of the hair collection protocol, some citing cultural beliefs. Among actual participants, few problems arose related to hair collection probably due to the culturally sensitive approach used during recruitment and measurement. Adult reports of exposure, hair nicotine, and hair cotinine showed considerable variation and were skewed to the right. Average concentrations of nicotine for these Latino children appear to be comparable to those reported elsewhere, while cotinine levels appear to be somewhat lower. Hair nicotine was more detectable than hair cotinine, and showed a clearer linear relationship with adults' reports than cotinine. However, associations between adults' reports and both biological measures were modest.

Collecting hair samples in the field (i.e., participants' homes) to measure Latino children's ETS exposure is feasible and generally acceptable when appropriate methods are used. Hair nicotine may be a more valid and practical biological measure than hair cotinine. Hair sampling may be a potentially useful, noninvasive technique in ETS studies, although the modest associations of constituents in children's hair with adults' reports indicate that each measure provides different information about ETS exposure.

G9

Anti-tobacco programming: reaching the deaf and hard-of-hearing

Partnering for tobacco control research among deaf youth

School-based anti-tobacco programs for deaf/hh Youth

Berman, Barbara, Wong, Glenn;[1] Kleiger, Heidi, Maucere, Lauren;[2] Guthmann, Debra[3]
1. University of California, Los Angeles (UCLA)
2. Greater Los Angeles Council on Deafness, Inc.(GLAD)
3. California School for the Deaf, Fremont (CSDF)

Understanding the patterns and determinants of tobacco use among socio-cultural subgroups of youth is critical in developing effective and targeted prevention strategies. Our research program seeks to understand how these tobacco use patterns and forces occur among Deaf youth and young adults, and to use this knowledge to shape effective anti-tobacco strategies for this population. Funded by the TRDRP, this research represents a first-ever effort to identify and address the tobacco control programming needs of this unique, understudied, and underserved population.

We report here on the multi-step nature of our research, which involves collaboration between tobacco control researchers at UCLA; leading community-based organizations serving the Deaf community in California, including the Greater Los Angeles Council on Deafness (GLAD), the California Coalition of Agencies Serving the Deaf and Hard-of-Hearing (CCASDHH); and a key educational institution serving deaf youth, the California School for the Deaf, Fremont (CSDF). Findings regarding tobacco knowledge, attitudes, practices and unmet program needs will be described from (1) an initial quantitative survey that was conducted among a sample of 467 deaf and hard-of-hearing (deaf/hh) children, adolescents and young adults, using both a written questionnaire instrument as well as a specially designed computer-based video technology for the deaf, the Interactive Video Questionnaire (IVQ™); (2) telephone interviews conducted among 45 administrators of residential and day schools for the deaf and of mainstream schools and colleges in California with large enrollments of deaf/hh youth; and (3) in-depth open-ended videotaped and transcribed in-person interviews conducted among a randomized sample of 40 students drawn from IVQ™ survey respondents. Finally, we will outline the steps being taken to use this information, based on these multifaceted data collection activities, to shape school-based tobacco control interventions for deaf youth and young adults.

H1

Age-dependent modulation of vulnerability to nicotine for the induction of atrial fibrillation

Karagueuzian, Hrayr S.
Cedars-Sinai Medical Center and
University of California, Los Angeles

Nicotine (N) has been implicated as a potential cause of a broad spectrum of cardiac arrhythmias including atrial fibrillation (AF). The factors responsible for N's variable influence on AF vulnerability remain undefined. We hypothesized that aging is one factor that modulates AF vulnerability to N.

Twelve male rats (Fisher-344) were grouped into young (2-4 months, N=6) and old (22-24 months, N=6). The isolated hearts were perfused (through the aorta) and superfused with oxygenated Tyrode's at 37°C. Atrial effective refractory period (ERP), interatrial conduction time (CT) and AF vulnerability (tested by burst atrial pacing) were then determined in both groups before and after 10-100 ng/ml N perfusion. [The arterial blood levels of N in smokers are between 30-85 ng/ml]. The epicardial surface of the atria was optically mapped using CCD camera.

At baseline, CT was significantly greater in the old than in the young rats (52±32 vs. 25±5 ms, P<0.05), however, there was no significant difference in the ERP between the two groups (19.2±4.8 vs. 19.3±7.6 ms). Burst pacing induced AF (CLs of 26-50 ms) in 5 of the 6 old rats. However, no AF could be induced in any of the 6 young rats. N increased interatrial CT and ERP in a concentration-dependent manner that was significantly (P<0.05) higher in the old than in the young rats (90±34 ms vs. 35±9 ms and 24±4 ms vs. 27±3 ms respectively during 80 ng/ml N perfusion). N at 10-30 ng/ml prevented AF induction in the old rats, however atrial tachycardia (AT) at CLs of 84-110 ms could still be induced in 5/6 old rats. N at 50 ng/ml and above caused loss of 1:1 atrial capture during regular pacing and prevented AF and AT induction in the old rats. In contrast however N at 10-100 ng/ml significantly (P<0.01) increased AF (N=3) and AT (N=3) induction in the young rats. Optical mapping showed the presence of 2-3 independent wave fronts during AF but only one large periodic wave front during AT. Old rats had significantly (P<0.05) greater interstitial atrial fibrosis compared to young rats (1.72±0.81 vs. 0.38±0.45%).

The mechanism of N-induced modulation of AF vulnerability is compatible with changes in interatrial CT and ERP. In atria with less than a critical increase in the CT/ERP (young rats at baseline) or excessive increase in CT/ERP (aged atria exposed to N >50 ng/ml) AF/AT can not be induced. Smoking-associated increase in atrial vulnerability to AF in man may be related to nicotine.

H2

Nicotine regulates cardiac toxicity with lipopolysaccharide

Bayna, Evelyn; Suzuki, Jun; Li, Hai Ling; Dalle Molle, Erminia; Lew, Wilbur Y.W.
University of California, San Diego

Nicotine inhibits apoptosis, or programmed cell death, an evolutionarily conserved method for removing excessive or potentially dangerous (e.g. cancer) cells. Apoptosis may be undesirable in the heart, where terminally differentiated cardiac myocytes cannot replicate to replace lost myocytes. Lipopolysaccharide (LPS) from gram-negative bacteria induces cardiac apoptosis, which may contribute to cardiac dysfunction in sepsis. It was hypothesized that nicotine inhibits LPS-induced apoptosis in cardiac myocytes.

Miniosmotic pumps were implanted in adult Sprague Dawley rats to infuse nicotine (6 mg/kg/day) or saline subcutaneously. After 7-10 days, LPS (1 mg/kg) or vehicle (control) was injected into the tail vein. This did not affect systolic blood pressure, as measured by tail cuff at 15, 30, 45 minutes, 1, 2, 4, or 24 hours after injection. After 24 hours, apoptosis was measured in the left ventricular myocytes by terminal deoxy-nucleotidyl transferase-mediated dUTP nick end-labeling (TUNEL) staining. LPS increased cardiac apoptosis in saline pump-treated rats (888 + 71 [SE] vs 551 + 71 positive nuclei / 10^6 nuclei in controls, P < 0.05, two-way ANOVA n = 6), but not in nicotine-treated rats (415 + 66 vs 502 + 78 positive nuclei / 10^6 nuclei, p = ns).

Similar results were obtained in cardiac myocytes exposed to LPS in vitro, in myocytes from rats pretreated with nicotine in vivo (pumps for 7-10 days) or in fresh isolated myocytes (from rats without pumps) exposed to nicotine (15 ng/ml) for 4-16 hours in vitro. For example in the latter case, LPS (10 ng/ml, 24 hours) increased apoptosis (4.0 + 0.4%) compared with control (2.6 + 0.4%) in saline-pretreated myocytes, but not in myocytes pretreated with nicotine for 4 hour (3.0 + 0.4% vs 2.8 + 0.3%) (P < 0.05, two-way repeated measures ANOVA, n = 10). One hour pretreatment with nicotine inhibited LPS-induced apoptosis partially, but not completely (P < 0.05, n = 10).

LPS induces apoptosis by activating cardiac angiotensin II, type 1 (AT_1) receptors. In myocytes isolated from rats with saline pumps, either LPS (10 ng/ml) or Ang II (100 nM) increased apoptosis after 24 hours (5.2 + 0.6% and 5.0 + 0.6%, respectively), compared with vehicle (3.4 + 0.5%) (P < 0.05, one way repeated measures ANOVA, n = 10). In myocytes from rats treated with nicotine pumps for 7-10 days, apoptosis increased with Ang II (5.1 + 0.8%) but not with LPS (3.6 + 0.4%) compared with vehicle (3.4 + 0.4%) (P < 0.01, n = 12). This suggests that nicotine inhibits LPS activation of AT_1 receptors in cardiac myocytes.

In conclusion, nicotine rapidly (within 1-4 hours) and completely blocks LPS-induced cardiac apoptosis in vivo or in vitro. These results are relevant not only in sepsis where LPS induces cardiac dysfunction, but also for subacute conditions where LPS can induce cardiac apoptosis without affecting blood pressure. Nicotine may provide a novel therapy for inhibiting cardiac apoptosis to preserve cardiac function.

H3

Carbon monoxide as a modulator of myocardial function

Kreutzer, Ulrike; Jue Thomas
University of California, Davis

Despite the awareness of carbon monoxide (CO) as a deadly poison in environmental tobacco smoke (ETS) and pollutant, the precise cellular damage remains an open question. In excess, CO will readily displace O_2 in blood, and the cells will just suffocate. This common view overlooks the interaction of CO within the cell. Even at very low concentration, CO can bind tightly to the intracellular oxygen storage protein, myoglobin (Mb) and might reduce the cell's ability to maintain a properly energized state. Such interaction with Mb could significantly affect heart function and may be a significant basis for the observed risk of heart disease in subjects exposed to ETS.

Perfused rat hearts receiving 10% CO, sufficient to inhibit 86% of the cellular Mb, exhibit no alteration in rate pressure product (RPP) or respiration. Only the lactate level increases. Under enhanced workstates, and thus enhanced demand for oxygen, similar observations emerge. Inhibition of Mb's oxygen carrying capacity during maximal stimulation with pacing and ß-adrenergic agents did not impact on heart performance or bioenergetic parameters. However, fatty acid appears to further stimulate lactate formation rate during CO inactivation. The data suggest that Mb inhibition affects metabolic regulation.

CO inhibition also appears to impact postischemic recovery. Although the recovered respiration, contractile function, and metabolic profile reveal no significant alteration with CO inhibition, the time to normal sinus rhythm, however decreases.

These experimental observations confirm the hypothesis that CO can directly interfere with cellular function. Further studies will continue to distinguish CO inhibition of Mb vs. a direct CO interaction in order to understand the mechanism underlying the observed cellular changes and to establish a firm basis to assess cardiovascular risk.

H4

Transgenic mouse model to investigate the atherogenic potential of human Lp (a)

Matthias Schneider, Erwin H. Ludwig, Kay S. Arnold, Thomas L. Innerarity and Robert E. Pitas
University of California, San Francisco

Smoking increases the risk of heart disease. Although the mechanism is not known with certainty, at least one study suggests that cigarette smoking increases plasma concentrations of lipoprotein(a) [Lp(a)]. High concentrations of low density lipoprotein (LDL) cholesterol is associated with an increased risk of premature heart disease. Lp(a), which consists of apolipoprotein(a) [apo(a)] bound to LDL, appears to be more atherogenic than LDL alone.

We hypothesized that the binding of Lp(a) to proteoglycans and plasminogen substrates in the arterial subendothelial space is critical to atherogenesis. To test this hypothesis, we began by generating LDL that binds poorly to artery wall proteoglycans. These proteoglycan-binding-defective LDL caused minimal atherosclerosis when expressed in transgenic mice fed a high-fat, high-cholesterol diet. Dr. Richard Lawn (CV Therapeutics) generated apo(a) that binds poorly to plasminogen substrates and is poorly retained in the artery wall when expressed in transgenic mice. We cloned this mutant apo(a) cDNA and a wild-type apo(a) cDNA into a liver specific vector and injected the resulting constructs into mouse embryos. Apo(a) was highly expressed in the liver of transgenic mice and plasma levels of mutant and wild-type apo(a) were 280 and 190 mg/dl, respectively.

We bred wild-type and mutant apo(a) mice with mice expressing wild-type LDL or proteoglycan-binding-defective LDL. In mice expressing both LDL and apo(a), most of the LDL was bound to apo(a) and circulated in plasma as Lp(a). These mice are being fed a high-fat, high-cholesterol diet to determine if proteoglycan-binding-defective, fibrin-binding-defective Lp(a) is less atherogenic than normal Lp(a).

Our studies will help explain the potent atherogenicity of Lp(a). Specifically, they will determine whether the binding of Lp(a) to proteoglycans and plasminogen substrates in the artery wall is an important first step in atherogenesis. The results will lay the foundation for inhibiting or preventing atherosclerosis with small molecules designed to inhibit the binding of Lp(a) to proteoglycans or plasminogen substrates.

H5

Vascular endothelial growth factor receptor signaling

Quinn, Timothy P.
University of California, San Francisco

Lung cancer and ischemic heart disease are leading causes of smoking-related mortality. The progression of both diseases is dependent, in opposite ways, on the growth or lack of growth of new blood vessels, a process termed angiogenesis. Rapid cancer growth is possible because tumors stimulate formation of new blood vessels to supply the tumor, while ischemic heart disease is most severe when the heart does not generate new collateral blood vessels to bypass occluded arteries. The angiogenic growth factor VEGF (vascular endothelial growth factor) is believed to be a central regulator of angiogenesis both in cancers and in ischemic tissues. Anti-angiogenesis and pro-angiogenesis therapies based on VEGF are already under investigation for treatment of cancer and heart disease, respectively. VEGF stimulates angiogenesis by turning on specific receptor proteins found in blood vessel cells. Our goal is to understand in molecular detail how the receptors for VEGF work.

VEGF binds to, dimerizes and activates two receptor tyrosine kinases: VEGFR-1 and VEGFR-2. It has been difficult to define the separate functions of each receptor, since both receptors are normally present in endothelial cells in culture and both are activated when cells are treated with VEGF. We have used an experimental system in which chimeric VEGF receptors are introduced into endothelial cells in culture. Chimeric VEGF receptors are composed of the extracellular domain of a different growth factor receptor that is not expressed in endothelial cells (the Fms receptor) fused to the intracellular signaling domain of VEGFR-1 or VEGFR-2. When the chimeric FmsVEGFR-1 or FmsVEGFR-2 receptor is expressed in endothelial cells, treatment with the Fms ligand dimerizes and activates only the chimeric VEGF receptor. This allows the functions of VEGFR-1 and VEGFR-2 to be separately investigated. Additional important features of this approach are that specific mutations can be introduced into the VEGFR domains of the chimeric receptors in order to define their functions, and that two different chimeric receptors can be co-expressed to explore receptor interactions. Using this approach we have found that two specific sites on activated VEGFR-1 associate with specific intracellular signaling molecules, including PLC-gamma, the p85 PI-3-kinase, and the Grb2 adaptor protein. Neither of these sites is required for VEGFR-1-mediated endothelial proliferation. We have further identified the site on VEGFR-2 where PLC-gamma1 binds, and have found that this site mediates prolonged activation of the MAPK signaling pathway and induces endothelial growth inhibition.

Future work will focus on identifying other intracellular signaling molecules that associate with and are activated by VEGFRs. Their binding sites on VEGFR-1 and VEGFR-2 will be identified by making additional receptor mutants. The role of these signaling molecules in VEGF-stimulated cellular responses such as endothelial proliferation and migration can then be determined. We will also investigate how heterodimers of VEGFR-1 and –2 function.

This work will define how VEGF, a key regulator of new blood vessel growth both in cancers and in coronary artery disease, works through its receptors to stimulate angiogenesis. This information will be useful for the design of new therapies for these tobacco-related diseases.

H6

Comprehensive evaluation of the ischemic leg

Nishimura, Dwight G.
Stanford University

The goal of this project is to develop magnetic resonance (MR) methods for a comprehensive evaluation of peripheral vascular disease, one of the major tobacco-use-related diseases. Under development are MR imaging tools to assess 1) lower extremity vessel anatomy, 2) total blood flow, and 3) regional perfusion.

For anatomic vessel imaging, we are studying three-dimensional (3D) imaging methods that rely not on contrast agents but on blood's intrinsic MR parameters or its flowing nature, to isolate the blood signal from surrounding tissue. One method uses a signal-generating sequence called steady-state free precession (SSFP), which produces high blood signal based on blood's MR relaxation parameters. A second method is a modified version of SSFP in which an oscillating dual-equilibrium is established, generating two images with significantly different signal levels depending on velocity.

For measurement of total blood flow in the leg, we are developing a new version of a popular MR technique called phase contrast (PC). This version provides a measurement of time-averaged velocity and flow by executing PC without any cardiac synchronization. Because cardiac gating is obviated, the sequence is fast (a few heart beats long) and convenient to apply. On femoral arteries, our initial experiments have shown the method to produce consistent flow measurements with an accuracy of about 10% and in scan times as short as two heart beats.

The third area of study is in regional perfusion measurement. We are developing a new fast scanning method that collects a time series of images over multiple slices, enabling the mapping and measurement of perfusion in the lower leg following an injection of a gadolinium contrast agent. The time series of images track the distribution of this contrast agent as it perfuses into the leg. Our initial results on human volunteers demonstrated the feasibility of quantifying muscle perfusion. The resultant spatial perfusion maps also showed regional heterogeneity in the muscle.

All of these methods will undergo further validation on phantoms and human subjects. We also plan new variations for the anatomic vessel imaging methods and the total flow measurement method. The perfusion method will be improved by increasing the number of slices with additional sequence optimization. For the assessment of tobacco-related peripheral vascular disease, these MR methods may provide a comprehensive set of clinically useful information that cannot be produced any other modality.

H7

Reduction in respiratory rate related hyperinflation as a guide for optimal lung volume reduction surgery in emphysema

Brenner, Matthew
University of California, Irvine

GOAL: There is a need for *intra-operative* measures to quantify and optimize the effects of lung volume reduction surgery (LVRS) procedures that are designed to improve breathing symptoms and function in patients with severe smoking induced emphysema. Dynamic hyperinflation (increased air trapping within the chest at rapid breathing rates required during exercise) is an objective physiologic measurement variable that closely correlates with subjective response to (LVRS) in emphysema patients. The goal of this study was to develop a method to measure the amount of dynamic hyperinflation in an emphysematous animal model before and after LVRS to be used as a potential guide to optimizing the amount of lung resection to be performed during surgery.

Hypothesis: We hypothesized that dynamic hyperinflation measured at increased respiratory rates (simulating exertional tachypnea) could be used to objectively assess effectiveness of LVRS in a rabbit model of emphysema.

WORK PERFORMED: Emphysema was induced in 25 New Zealand White rabbits. Resting lung function measurements were obtained prior to induction of emphysema, immediately prior to bilateral staple LVRS, and 1 week post-operatively. Dynamic hyperinflation was measured in mechanically ventilated rabbits at normal respiratory rates (32 BPM) then at rapid ventilation rates (50 BPM) simulating exercise. The improvement in dynamic hyperinflation following lung volume reduction surgery was assessed as a function of the amount of lung resected.

Results: There was a significant increase in air trapping at rapid ventilation rates following induction of emphysema in comparison to baseline (10.7±1.03% trapping with emphysema versus 6.76±0.54% baseline normal rabbits before emphysema, p=0.003), which normalized following LVRS (6.26±0.75% post-LVRS, p=0.002 compared to emphysema pre-op).

Conclusions: Respiratory rate related dynamic hyperinflation occurs with development of emphysema in this model (analogous to humans) and improves following LVRS. The reduction in dynamic hyperinflation can be readily measured.

FUTURE DIRECTIONS: Intraoperative dynamic hyperinflation improvement measurements must now be correlated with long term lung function improvements both at rest and with exertion in the models in order to determine the optimal resection volumes. Such studies are underway at this time. Ultimately, analogous methods developed in this research project need be studied in patients with emphysema undergoing LVRS.

SIGNIFICANCE: At the present time, there is no method for determining how much lung tissue should be resected during LVRS surgical procedures in emphysematous patients. This is a very important question since excessive resections may lead to deterioration of lung function, while suboptimal resection volumes may result in minimal response. The measurement of dynamic hyperinflation intra-operatively by hyperventilatory rate simulations might be a potentially important guide to optimize LVRS resection in severely debilitated emphysematous patients. Objective methods for optimizing LVRS would likely have substantial impact on quality of life, survival, morbidity, post-operative LVRS costs, and long-term productivity of very debilitated emphysematous patients.

H8

Therapies for muscle dysfunction in COPD

Casaburi, Richard; Cosentino, Louis; Porszasz, Janos; Bhasin, Shalender; Storer, Thomas
Harbor-UCLA Research and Education Institute

It was the aim of this project to improve the effectiveness of treatment for people with lung disease produced by cigarette smoking. Chronic obstructive pulmonary disease (COPD, also called emphysema or bronchitis) afflicts approximately 14 million people in the United States. It is a disabling disorder and inability to exercise is usually the foremost problem. It is now clear that these patients suffer not only from poor lung function but from poor muscle function as well. We focused on strategies intended to improve the muscle's ability to tolerate exercise. Two strategies were explored. First, in men the naturally occurring body chemical, testosterone, is important in maintaining muscle mass. Many men with COPD have low testosterone levels. We determined whether administering testosterone to COPD patients increases muscle mass and strength as we have demonstrated in healthy young men. Second, we determined whether a conditioning program consisting of a group of weight lifting exercises improves muscle strength.

We recruited a total of 52 men with COPD; 47 completed the protocol. They were assigned by chance to one of four groups that received: no strength training and no testosterone, strength training (for one hour a day three times per week) but no testosterone, testosterone (100mg of testosterone enanthate intramuscularly) but no strength training, or both strength training and testosterone. A large number of state-of-the art measurements were made before and after the 10 week study period. On average, subjects had severe COPD (FEV_1=40% predicted); the interventions did not change measures of pulmonary function in any group. Testosterone levels on entry were low; subjects receiving testosterone doubled nadir blood levels to the middle of the normal range for young men. Both LH and FSH levels were supressed to near zero, indicating that endogenous testosterone secretion was inhibited. In the groups receiving testosterone, whole-body muscle mass (assessed by DEXA scan) increased; in the group receiving strength training alone, muscle mass of the legs increased. The group receiving the combined intervention had a 3.3kg (6.3%) increase in muscle mass and an average decrease in fat mass of 1.5kg (6%). Strength of the thigh muscles (measured by 1 repetition maximum of the leg press exercise) increased both in the groups receiving testosterone alone and strength training alone; the group receiving the combined intervention experienced an average 23.3% increase in strength. As expected, measures of exercise endurance, assessed by cardiopulmonary exercise testing, did not improve. There were no adverse effects of these interventions; specifically no hepatic or prostatic side-effects were observed and the lipid profile was not altered.

These findings suggest that both strength training and testosterone supplementation will be beneficial additions to programs of pulmonary rehabilitation for patients with COPD and, thereby, help patients suffering from this smoking-related disease.

H9

Expression and localization of nicotinic acetylcholine receptors in airway smooth muscle in developing mouse lung

Wuenschell, Carol
University of Southern California

Contraction of smooth muscle in the lung is believed to be mediated by acetylcholine interacting with acetylcholine receptors of the muscarinic type localized on airway smooth muscle, and vascular smooth muscle cells. Our previous studies with nicotine exposure of embryonic lung buds in organ culture have shown that nicotine directly affects lung development. This effect is mediated by the other class of acetylcholine receptor - the nicotinic acetylcholine receptor (nAChR). NAChRs comprise a diverse family of receptors whose members have been found on skeletal muscle, nerve cells and some neuroendocrine cells. Although the lung is known to contain neurons and neuroendocrine cells, little is known regarding the nature and location of nAChRs in the lung.

At least ten genes encode subunit proteins that join together in various combinations to form the pentameric nAChRs found on neurons and other cell types. We used a semi-quantitative RT-PCR based method to investigate the expression profiles of the nAChR subunits designated α1, α2, α3, α4, α5, α6 α7, α9, β2, β3 and β4. Lung from gestational day 12 mouse embryos showed expression of α3, α4, α7, β2, and β4 subunits. Lower levels of the α5 and α9 subunits were detected under more sensitive conditions. The a1 subunit, a skeletal muscle nAChR subunit used as a negative control, was not detected at any stage even under the most sensitive conditions. Expression levels of each nAChR subunit detected in the early embryonic lung were examined in a developmental series extending through late gestation to early postnatal and adult. The nAChR subunits α3, α4, α7, and β4 were expressed most abundantly in early embryonic lung with the level gradually declining toward the postnatal stage. Expression persisted in the adult lung at very low levels. The nAChRs α5, α9, and β2 were present at low levels with little variation throughout the developmental stages. To localize the receptors, three monoclonal antibodies (Mabs) obtained from Covance were used: Mab319 reacts with the α7 subunit, Mab210 reacts with the three subunits α1, α3, and α5, and Mab270 reacts with the β2 subunit. All three monoclonal antibodies localized the receptors to smooth muscle surrounding the large airways and not to neurons, or vascular smooth muscle as shown by comparison to localization patterns of marker proteins specific for smooth muscle or for neuronal cell types.

The role of nAChR in airway smooth muscle is uncertain and will be the focus of future studies. A preliminary study with an α7 blocker showed that nAChRs might be involved in regulation of gene expression related to smooth muscle cell proliferation in airways. Abnormal airway smooth muscle cell proliferation may be important in asthma and chronic obstructive pulmonary disease. The potential action of nicotine on airway nAChRs raises the possibility that such receptors could be involved in tobacco-related lung pathology in humans resulting both from pre- or postnatal passive exposure and from active exposure in adult smokers.

H10

Genetic deficiency of human mast cell a-tryptase

Soto, Darya
University of California, San Francisco

Mast cells are inflammatory cells that reside in various tissues, including the airways, and synthesize and secrete inflammatory factors, growth factors and enzymes. One such family of enzymes are the tryptases, which cleave other proteins at basic amino acid residues. There are several types of tryptases, all of which reside in a cluster on human chromosome 16. Alpha-tryptase is not stored inside the cell but is constitutively secreted. However, it is released in an inactive form. To date, there is no known function of α-tryptase in humans. Beta-tryptases, on the other hand, are secreted in the active form and are the tryptases implicated in pulmonary and allergic disease.

Our laboratory has mapped and aligned tryptase genes. Based on our results, we propose that α-alleles compete with some β-alleles at one locus and that an adjacent locus contains β-alleles exclusively. This hypothesis predicts that β-alleles outnumber α and that some individuals lack α genes altogether. To test this hypothesis, we developed polymerase chain reaction-based techniques to distinguish α from β genes. We then genotyped DNA from 271 people and four immortalized tryptase-expressing cell lines. In support of our hypothesis, we find that α-tryptase deficiency affects 28% of individuals surveyed and that overall α-allele frequency is 0.24. Thus, as predicted, β alleles outnumber α. In samples of known ethnicity, α deficiency occurs in 26% of African-Americans and 42% of Caucasians, but in only 15% of other backgrounds. Examination of cell lines reveals that HMC-1 and U-937 lack α-genes. By contrast, α-transcribing Mono Mac 6 and KU812 cells contain α- and β-genes. Thus genetic α-tryptase deficiency is common and varies strikingly between ethnic groups.

Because β (but not α)-tryptases are implicated in pulmonary disorders, inherited differences in α/β-genotype may affect disease susceptibility, severity and response to tryptase inhibitor therapy. Our future direction is to compare asthmatics versus normal individuals. We plan to correlate α/β-tryptase genotype with asthma severity and propose that we will see more severe disease in individuals who have more β versus α-genes. If this is the case, then these more susceptible individuals may have a favorable respond to anti-tryptase therapy.

H11

Regulation of lung inflammation by the LTC_4 synthase pathway

Serio, Kenneth J.
VA San Diego Healthcare System and the University of California, San Diego

Tobacco use has been demonstrated to increase the risk of bacterial lung infection. The current proposal examines the effect(s) of the bacterial component, lipopolysaccharide (LPS), on leukotriene C_4 (LTC_4) synthase gene expression in mononuclear phagocytes. The synthesis of LTC_4 is the first committed step in the synthesis of the cysteinyl leukotrienes, LTC_4, LTD_4, and LTE_4. These mediators are known to account for a variety of inflammatory responses. LPS acts through Toll-like receptors (TLRs) to elicit a localized proinflammatory response involving monocytes/macrophages that may promote host defense against bacterial infection.

Conditioning of THP-1 cells for 7 days with *S. minnesota* Re 595 LPS (Re LPS) at 10 ng/ml resulted in decreased LTC_4 release in response to stimulation with the calcium ionophore, A23187 (at 1 µM). By RT-PCR, the monocyte-like cell line, THP-1, was found to express both TLR2 and TLR4. Conditioning of THP-1 cells with 1 µg/ml of *E. coli* 0111:B4 smooth LPS (0111 LPS) for 24 hrs resulted in a significant decrease in LTC_4 synthase mRNA, as detected by Northern blot analysis. Conditioning of cells with 0111 LPS and Re LPS at 10 ng/ml resulted in a decrease in LTC_4 synthase mRNA. Northern blot analyses with varying doses of Re LPS indicate that LPS dose-dependently downregulates LTC_4 synthase mRNA. Time course Northern blot analyses demonstrate that the LPS-induced decrease in mRNA was time-dependent, resulting in suppression of mRNA as early as 4 hrs. Cycloheximide conditioning of LPS-treated THP-1 cells for 24 hrs did not inhibit the LPS effect on LTC_4 synthase mRNA, suggesting that synthesis of a new protein transcription factor was not required. Transient transfection of THP-1 cells with a luciferase reporter construct containing the first 1.35 kb of the LTC_4 synthase promoter with subsequent LPS conditioning demonstrated that gene transcription is downregulated. Further work will attempt to identify the mechanism(s) of action of LPS on the expression of the LTC_4 synthase gene and its products.

We suggest that the effect of LPS on LTC_4 synthase gene expression may have implications for monocyte/macrophage-mediated host defense against bacterial infection in the pathogenesis of tobacco-related inflammatory lung diseases such as asthma and COPD.

H12

Chronic bronchitis: pathology of mucin gene expression

Rheinhardt, JM. and Finkbeiner, WE.
University of California, Davis

The long-term objective of these studies is to increase our understanding of the role that mucins play in tobacco-related chronic bronchitis. Mucins make up a large part of mucus, the complex, heterogeneous secretion that helps protect the lung from infection and injury. In chronic bronchitis, mucus production is increased. The objectives of this project are to determine 1) which mucin genes are upregulated in smokers; 2) which lung cells produce the specific mucins; and 3) which inflammatory cells and inflammatory mediators are involved in this process. To aid in achieving these objectives, we investigated if differences in peptide bond cleavage caused by two proteolytic enzymes, proteinase K and protease XXIV, affected detection of mucin gene expression in archival tissue using in situ hybridization (ISH). Five mucin riboprobes, MUC2, MUC5AC, MUC5B, MUC6, and MUC7 were evaluated. We used samples representing the tissues from which each mucin gene was cloned originally. We used colon tissue for MUC2, bronchus for MUC5AC and MUC5B, stomach for MUC6 and submandibular gland for MUC7. Reactivity of mucin gene mRNA product as detected by ISH was quantified by image analysis using an imaging workstation (TriPath, Burlington, NC) and software (Image Pro, Media Cybernetics). An area of interest was selected on a slide (either Protease XXIV or Proteinase K treated) and an image captured. The corresponding field on the adjacent section treated with the other proteinase was located and its image captured. Using the image analysis software, the percentage of the area that contained reaction product was determined for each protease. At least five fields per slide were compared. Results were analyzed using a paired t-test. For each mucin, the amount of mucin mRNA as detected with ISH was increased with Protease XXIV. For each mucin, the amount of mucin mRNA as detected with ISH was increased with Protease XIV. With MUC5AC, ISH with proteinase K was not sensitive enough to detect any target mRNA. For the remaining mucin genes studied, the increased sensitivity when using protease XXIV ranged from 1.5 to 2.7 times greater than when proteinase K was employed. Thus, we found protease XXIV to be the enzyme of choice for protease digestion of archival tissue when used for detection of human mucin gene expression. Overall, the knowledge gained from the studies proposed in this application will lead to a better understanding of biological role of mucin in tobacco-induced chronic bronchitis and its complications. This may lead us to medical interventions to counter the excessive production of mucus characteristic of this disease.

H13

Environmental tobacco smoke induced changes in lung surfactants

Zasadzinski, Joseph
University of California, Santa Barbara

The short term effects of exposure to environmental tobacco smoke are less known than the long term or epidemiological effects. We are interested in the effects of short time exposure of environmental tobacco smoke on the surfactant lining of the lungs. Our in vitro model of the lungs is a Langmuir trough, filled with a saline subphase, onto which we spread monolayers of natural or synthetic human lung surfactant. The saline subphase is similar in composition to the liquid that lines the alveolar spaces within the lung. To determine the effects of various levels of environmental tobacco smoke on surfactant, we expose the saline subphase to aged and diluted sidestream cigarette smoke (ADSS) for various times and various concentrations prior to spreading the surfactant monolayers. Pressure-area isotherms and fluorescence microscopy measurements reveal that both the physicochemical parameters of the phase transition of model lung surfactant monolayers and the morphology of the condensed phases at high lateral pressures are significantly different on the subphases depending on the level of exposure to ADSS.

This study was designed to determine whether the exposure to ambient levels of aged and diluted sidestream cigarette smoke (ADSS) to the sub phase used in monolayer studies would alter the phase behavior of model lung surfactant lipids. In our measurements, we used lipid mixtures that are able to serve as surfactant replacements. In order to elucidate the influence tobacco smoke constituents on the surfactant monolayer the results are compared with those obtained on tobacco smoke exposed systems. The results show that upon ADSS exposure the model system exhibits a lower respreading capability of the collapsed monolayer. Moreover, fluorescence microscopy revealed an irreversible formation of condensed phase domains after multiple compression and expansion cycles. These results suggest that tobacco smoke exposure to the lung surface reduce the performance of the lung surfactant monolayers. Hence, altered physicochemical behavior of native lung surfactant monolayers must be expected. The most likely outcome is a more viscous monolayer and a larger work associated with breathing.