

# Burning Issues

Tobacco's Hottest Topics

Tobacco-Related Disease Research Program Newsletter

Special Edition

October 2005

Key Brain Protein in Nicotine Addiction Identified by TRDRP

## 15 Years of Progress in the Fight Against Tobacco

African American and Latino Youth Shown to have Easier Access to Tobacco Products

Internal Documents Expose Tobacco Industry Deception

SIDS Linked to Smoking by California Researcher

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Research proves Secondhand Smoke to be a Class A Carcinogen

# TRDRP: Focusing Research on Tobacco for a Healthier California

Charles DiSogra, Dr.P.H., M.P.H.

The lens is a frequently used metaphor for how we view the world or bring focus onto a subject. Before the creation of the Tobacco-Related Disease Research Program (TRDRP), there was no defined focus in California on tobacco-related research. In 1988, the enabling legislation for the newly passed Proposition 99 was being prepared. At the time, this legislation was truly revolutionary. It was a sweeping tobacco control directive for the state, a mandate that existed nowhere else in the country or the world. In conjunction with this, the framers astutely created a new funding program to focus significant scientific research on the devastating problems associated with tobacco. That funding program is TRDRP—the lens to bring that focus on tobacco to California scientists.

### The beginnings

In 1990, TRDRP awarded its inaugural grants. A tax on tobacco products, 25¢ per pack of cigarettes, generated \$878 million in 1989–90. Five percent of that, \$43.6 million, went to a research account allocated to the University of California to establish and administer TRDRP. The fledgling organization was underway, but the problems were just beginning. It seems that not everyone shared the vision for TRDRP.

The tobacco industry made attempts through its supporters at the time to dilute the efforts of this organization. They wanted spending limited to only the University of California campuses and the money used just to support “hard” research. In effect, they did not want TRDRP to fund policy, economic, social science, and behavioral research. Keeping research “in the laboratories” was considered to be much less threatening to tobacco industry interests<sup>1</sup> (a premise later to be proved erroneous with, for example, the emergence of secondhand smoke research). That challenge ultimately failed and those limits were never imposed.

The young and ambitious TRDRP rapidly brought a visible focus on tobacco-related disease and tobacco control research, including studies revealing unsavory tobacco industry tactics. The response from the tobacco industry and its allies among lobbyists and elected officials in state government was equally rapid. Funding was halted in 1994, as then governor Pete Wilson attempted to use the research funds, some \$21 million, for other state programs. A successful lawsuit against this action brought by anti-tobacco advocates based in California, notably the American Lung Association, the American Heart Association, American Cancer Society, and Americans for Nonsmokers Rights had the funds restored and the program resumed in 1996.

### Funding the best

The restored funds plus the 1996 tobacco products surtax revenue made Cycle 5 a windfall for tobacco-related disease research in California, with over \$60 million being available for grants. American satirist P. J. O’Rourke once quipped, “Giving money and power to government is like giving whiskey and car keys to teenage boys.” Not so with TRDRP grant money administered by the University of California. The Proposition 99 legislation instructed the university to institute a competitive grant application and review process similar to that used by the National Institutes of Health (NIH).

The NIH model has been the paradigm for TRDRP’s application review process. With this process, relevant applications are assigned to expert review panels made up of scientists from outside of California (designed to minimize conflicts of interest). These panels discuss and then rate each application with a scientific merit score. The score is then used as the primary basis for recommendations to be made by TRDRP’s Scientific Advisory Committee (SAC). The SAC consists of California scientists, none of whom can receive TRDRP grant money during their three-year tenure. The result is that the best of the best are funded across a breadth of scientific disciplines. Once funded, TRDRP staff scientists along with grant analysts monitor each study routinely over its lifetime for both scientific and fiscal progress and integrity.

Generally, research follows the money. TRDRP is one of the nation’s largest funders of tobacco-related disease research, perhaps second only to the NIH. The breadth of TRDRP’s research portfolio is the strength that has defined it over time. The action has been both inside and outside the laboratory, in communities and schools, in the archives of tobacco industry documents, pushing the envelope to advance knowledge and building a tobacco-focused research infrastructure for California. So what have 14 funding cycles brought to light with this California focus on tobacco? And what has been built over the years with over 1,100 grants funded and \$366 million invested?

### Advancing science

Funding biomedical and laboratory research has been essential for scientific progress toward improved treatments for the diseases identified as TRDRP’s mission. These diseases are cancer, cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, and nicotine addiction. One example is the genetic engineering of mice that had led to the seminal 2004 discovery of the neuroprotein

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## TRDRP

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responsible for nicotine addiction.<sup>2</sup> Another is the important laboratory work that led to the discovery of the complex mechanism by which components of tobacco smoke cause arterial plaque formation.<sup>3</sup> The studies of lung tumor vasculature led to the development of a novel DNA vaccine that deprives tumors of their blood supply thus inhibiting cancerous growth.<sup>4</sup> Inherited gene deficiencies are now being suspected as the reason why some people may be more prone to the harmful effects of smoke and other inhaled irritants and allergens than others. Persons with this condition have an increased susceptibility to tobacco-related pulmonary pathologies such as chronic obstructive pulmonary disease (COPD).<sup>5</sup>

The list of achievements is long and extraordinary and includes impressive work on the mechanisms of how active and passive smoke contributes to infertility, impaired fetal development, and spontaneous abortion. One of the most recent areas being studied shows that exposure to tobacco smoke can lead to hearing loss in infants.<sup>6</sup> These reproductive and developmental effects have provided compelling information to advance policies for the control of second-hand tobacco smoke, especially regarding exposure of young women, pregnant women, infants, and children in general.

### Shaping policy

Over the last four funding cycles, some 40% of TRDRP grants have addressed public policy, economics, epidemiology, and social and participatory research topics. These have been and are critically important to tobacco control and have been an integral part of TRDRP's overall portfolio since the program's inception. In the program's nascent years, a grant to UCSF was part of the seed money that gave birth to the nationally recognized tobacco industry documents library. That beginning was later leveraged into a \$15 million award from the American Legacy Foundation to establish the Legacy Tobacco Documents Library widely used for policy research. Also funded by TRDRP were the first California-specific economic studies that estimated health care costs of tobacco use in combination with other related costs such as lost productivity—an astounding total of \$16 billion annually.

TRDRP has been a leader in contributing to tobacco control in this state by funding needed population-based investigations. Descriptive epidemiologic studies of tobacco-use, plus research on control strategies and smoking cessation efforts among the many diverse population groups in California are numerous. This includes the program's involvement with national research on mentholated cigarette use among African Americans.<sup>7</sup> TRDRP studies have been funded to examine the cultural dimensions of tobacco-use and prevention strategies for Asian groups, such as Chinese, Vietnamese, Korean, Hmong, Laotians, Cambodians, Filipinos, and also for Pacific Islanders. Research in the rap-

idly growing and diverse Latino population has been and continues to be an equally important focus. Additionally, recently funded work will be looking at the harmful practice of hookah smoking among Arab Americans. One group with smoking rates in the 30–50% range and in need of more effective intervention is California's lesbian, gay, bisexual, and transgender (LGBT) community. TRDRP funded the first large-scale LGBT studies confirming these high rates. Another group with similar high smoking rates and where intervention research remains deficient are people of American Indian/Alaska Native heritage.

### Applied research

Anyone who has conducted research in the community or the classroom, knows that these are complex laboratories. What has evolved over the years is a collaborative approach to conducting tobacco-focused research with a community or with a school. TRDRP was one of the first funding agencies to encourage and fund what is known as participatory research by encouraging and funding academic researchers and either community groups or schools to work in partnership to explore effective tobacco control or cessation interventions. This approach has been used with Asian, African-American, and Latino communities and in the development of a cessation intervention for diverse groups of teens in school settings. For qualified school-based studies, the California Department of Education provides additional funding for the schools involved. Overall, funding well-executed participatory research is desirable in order to more effectively advance the science for tobacco control in California.

### Secondhand smoke

From the laboratory to the policy arena, TRDRP has brought the needed focus on the topic of secondhand smoke (SHS) for California and for the nation. Some of the important studies funded by TRDRP demonstrated the deleterious effects of SHS on heart disease, stroke, lung function, reproductive health, and fetal development. Many of these results were first brought into policy focus in the long contentious battle to pass California Assembly Bill 13 in January 1994. The passage of AB13 was a policy success over the strong opposition of the tobacco industry. TRDRP science was an important contributor to arguments in support of this historic bill.

Secondhand smoke or “passive smoking” was an issue of growing concern among a health-conscious public in California. It was definitely on the radar for the California Environmental Protection Agency (EPA). Findings from TRDRP-funded scientists were available when the California EPA designated SHS as a Class A Carcinogen (i.e., in the same category as mustard gas, arsenic, and asbestos),<sup>8</sup> a substance known to cause cancer in humans. Other research funded by TRDRP significantly advanced our knowledge on the physical dynamics of SHS, including biological absorp-

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# Tobacco Research Translation Institute

## Research Translation for the Advancement of Tobacco Control

Francisco O. Buchting, Ph.D.

The Tobacco Research Translation Institute (TRTI) is a new program initiative by TRDRP with the goal of facilitating the translation, dissemination, and application of research findings among tobacco control professionals and the larger public health community. The TRTI has been designed to complement the TRDRP Conference 2005 so that institute participants can also take advantage of the general conference program.

It is a reality that tobacco-related research has been, and undoubtedly will continue to be, a key weapon in the battle against tobacco use and tobacco industry tactics. This has been, in part, due to the tobacco industry misusing and manipulating scientific research to block or derail tobacco control efforts. In fact, this tactic continues to be a key tool for the tobacco industry in their anti-tobacco control agenda (see Buchting, F.O., *Burning Issues Research is Vital for Tobacco Control*. April 2004.)

The antidote to the tobacco industry's reprehensible use of science has been to use empirically validated scientific findings to expose and counter their campaigns of misinformation and deception while advancing tobacco control policies. Given the importance of research in tobacco control, it is important to have more than a single conduit or model for research findings published in the scientific literature to be "translated" and applied for public health purposes.

### Translation—A matter of semantics

What is meant by research translation, translational research, or translating research depends on where in the research enterprise those words originate and from whom, e.g., scientists, health care providers, public health professionals, funders of research, or administrators. The most familiar meaning of research translation is part of the National Institutes of Health's "Roadmap" for medical research in the 21st century. In this instance, translational research refers to the concept of bench-to-bedside, i.e., move basic scientific discoveries to clinical trials and ultimately into standard health care practices. Likewise, the National Cancer Institute's 3Ds initiative (Discovery, Development, and Delivery) is another example of major efforts being done at the federal level in the area of research translation. For tobacco control purposes, the meaning of research translation also includes the dissemination of robust and empirically validated research findings in such a way where they can readily be used to advance tobacco control efforts and policies. Due to the significant role research findings play in tobacco control, research translation has an important role in the ongoing work.

The issue of translating research findings for tobacco control purposes has received some attention at the national and local levels. This issue continues to be discussed at different research and tobacco control conferences. Funders, scientists, and tobacco control professionals find themselves in a quandary as to which is the optimum method to do the research translation and who should be paying for it. In the meantime, different efforts and programs continue to make concerted headway in the area of research translation in order to strengthen tobacco control efforts and policies.

### Research translation for tobacco control

For over 15 years, the TRDRP has been the leader in funding scientifically sound tobacco-related research that is vital for tobacco control efforts in California. At the same time, TRDRP has also created and funded initiatives to disseminate research findings. A few examples are TRDRP's publications such as the *Burning Issues* newsletter and the 10-year Research Summary, innovative award mechanisms in the area of participatory research, and focusing the 2003 Annual Investigator Meeting on the issue of "investigating, translating, and disseminating" research findings. In addition, part of TRDRP strategic planning has included convening expert panels of tobacco control professionals to advise the program on how to better meet tobacco control needs. And now, the TRTI is one of the most direct initiatives of TRDRP in the area of research translation for tobacco control.

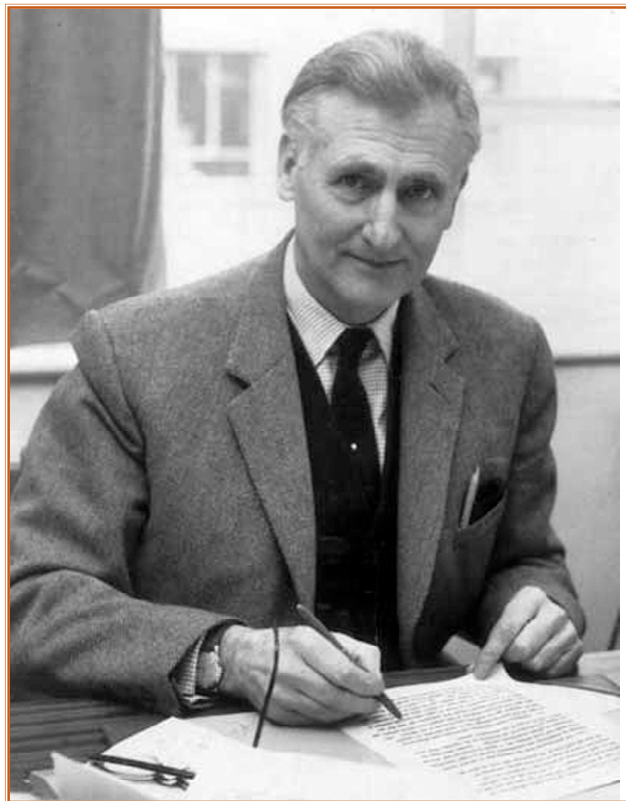
The goal of the TRTI is to create a track at the TRDRP Conference 2005 to translate mainly the TRDRP-funded research by bringing together tobacco control professionals and scientists. The research translation sessions at the TRTI will focus on two specific areas: 1) secondhand smoke; and 2) reproductive health effects of tobacco exposure. The TRTI will provide the format and forum for a dialogue between leading scientists in specific research areas and tobacco control professionals. In addition, each TRTI participant will be provided with a tool kit designed to aid in the dissemination and application of the scientific content from the TRTI's research translation sessions.

TRDRP continues to make research translation a part of the program's mission with the goal of contributing and strengthening tobacco control efforts in California. The TRTI represents one of the latest cutting-edge initiatives in the evolving area of research translation for public health purposes.

# SIR RICHARD DOLL (1912-2005)

## The Man Who Started it ALL

M.F. Bowen, Ph.D.



The man who provided the definitive confirmation of the causal link between smoking and lung cancer died on July 24, 2005 at the age of 92. Professor Sir Richard Doll, with his mentor and colleague Professor Austin Bradford Hill, showed that the incidence of lung cancer was directly proportional to the number of cigarettes smoked. The finding has saved the lives of millions. At the time, the results were so compelling that Sir Richard himself quit smoking two-thirds of the way through the preliminary study. In 1971 he was knighted for his work, which culminated just last year in publication of the results of his unprecedented 50-year study of smoking and death among British doctors. It showed that although smokers die an average of 10 years sooner than nonsmokers, those who quit even up to the age of 50 can still cut their risk of smoking-induced premature death by half.<sup>1</sup>

If “research is the art of seeing what everyone else has seen and doing what no one else has done,” then Sir Richard’s work ranks as one of the great research accomplishments of all time.<sup>2</sup> Richard Doll was not only responsible for this, one of the outstanding public health accomplishments of the 20th century, but his work also had implications

for epidemiological methodology, as well as the rise of social-behavioral science, noncommunicable disease epidemiology, and socio-political medicine. Major media, including the BBC, The New York Times, and Time magazine, as well as the United Nations and the World Health Organization noted his passing. Tributes poured into the BBC from around the world. Who was Richard Doll and how did he become one of the strongest scientific voices in the fight against tobacco?

### When one door closes . . .

William Richard Shaboe Doll was born in Hampton, England on October 28, 1912. His father wanted him to become a doctor but his love of mathematics prompted him to take the mathematics entrance exams at Trinity College. Unfortunately, his over-indulgence at a student beer bash the night before caused him to flunk the exams.<sup>3</sup> So acceding to his father’s wishes, he trained as a doctor and graduated from St. Thomas Medical School London in 1937.<sup>4</sup> He intended to become a brain surgeon but World War II intervened, and by the time his service in the Royal Army Medical Corps ended, it was too late to begin the long and arduous training necessary for neurosurgery. Instead he combined his love of mathematics with his chosen profession and became an epidemiologist.<sup>5</sup>

He had the good fortune to take a course in medical statistics at the London School of Hygiene and Tropical Medicine and thus met Austin “Tony” Bradford Hill, who was teaching the course. Professor Hill was also the eponymous originator of the widely cited “Hill’s Criteria of Causation,” which laid out the minimal conditions necessary to establish a causal relationship between two phenomena, a cornerstone of epidemiological research to this day. Hill asked Doll to work with him on a project aimed at determining the cause of lung cancer. Deaths due to lung cancer had been increasing in the decades since the turn of the century. In fact, Britain had the highest lung cancer rates in the world in the 1930s.<sup>6</sup> But the carnage attendant on two world wars diverted attention away from the epidemic. By the time Doll and Hill started their work at the British Medical Research Council, public health officials were alarmed enough by this mysterious epidemic to make funding available for research into its cause. So began Sir Richard’s long and illustrious career in the fight against tobacco.

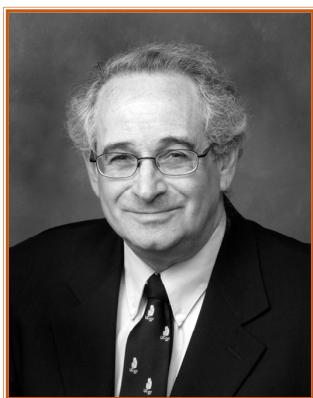
### Decoding the lung cancer enigma

Reports that smoking caused lung cancer had appeared as early as 1912.<sup>6</sup> However, as Sir Richard noted, “. . . the

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# Those Who Are Outstanding. . . .

*As part of our 15-year anniversary of funding cutting-edge tobacco research, TRDRP is taking stock of our accomplishments and the challenges ahead. The positive recognition that TRDRP receives is first and foremost a function of the science and the scientists we fund. In this regard, TRDRP has identified six scientists whose contribution to tobacco-related disease research has been nothing short of outstanding. TRDRP recognizes that the investigators we profile below are just a few of the dozens of women and men who have made exemplary achievements in the fight against tobacco. These six researchers span the breadth of TRDRP's extensive portfolio: cancer research and cellular biology; the neuroscience of nicotine addiction; tobacco-industry documents research; fertility and reproductive health; secondhand smoke; cardiovascular health; and health disparities among California's diverse populations. Phil G. and Kamlesh A.*



**Stanton Glantz, Ph.D.**, is arguably one of the most recognized names in tobacco research in the world and a constant thorn in the side of the tobacco industry. It was TRDRP that funded his initial ground-breaking work on secondhand smoke that not only detailed its impact but also exposed the hypocrisy and deceptions of the tobacco industry on this subject. Stan, as he is known in the field, has been part of the California anti-smoking movement for the past 25 years. He is one of the co-founders of Americans for Nonsmokers Rights and helped write and produce the film "Secondhand Smoke." Dr. Glantz is the author of three books and 150 scientific papers and lectures around the country and throughout the world. However, it was the publication of "The Cigarette Papers," in 1996 that set the field on fire and launched a whole new branch of tobacco control exploration: tobacco industry documents research. For the first time, the tobacco industry's lies and falsifications were exposed by using the industry's own words and writings. He revealed that the tobacco industry knew that nicotine was addictive and that smoking causes cancer, and they knew this since the 1960s. The publication of this book coincided with a series of successful grant applications

to the TRDRP, emanating from the team of researchers led by Dr. Glantz that culminated in a multimillion dollar grant from the American Legacy Foundation to permanently establish and house the UCSF Tobacco Control Archives. TRDRP is proud to have sponsored and supported the development of this resource that is used by scientists and tobacco control advocates around the world. In fact, Dr. Glantz's efforts to lay bare the manipulations of the tobacco industry have been so successful that he, the University of California, and TRDRP have been sued twice by the tobacco industry (both times unsuccessfully)!

Stan is currently the Director of the Center for Tobacco Control Research and Education at the University of California San Francisco and says, "It was TRDRP that got me started down this road. TRDRP was ahead of the curve, ahead of the National Cancer Institute, and ahead of all the other tobacco research funding agencies; it was you guys who were the first to give investigators funds to expose the tobacco industry."

**Steven M. Dubinett, M.D.**, professor of medicine and director of Jonsson Comprehensive Cancer Center Thoracic Oncology Program at UCLA, is a prominent clinician scientist who had made significant contributions to myriad aspects of translational research on lung cancer. Dr. Dubinett received a New Investigator Award from TRDRP in its very first funding cycle and subsequently also won an IDEA award and two Research Grant awards from us. The current focus of his research is to assess the impact of tumor cyclooxygenase-2 in lung cancer growth, invasiveness, angiogenesis, immunity, and apoptosis in non-small cell lung cancer. Dr. Dubinett and colleagues have a very productive scientific track record and their research papers, more than 30 in the last three years, have added significantly to the body of knowledge on the immunotherapeutic approaches for lung tumors. In addition to these impressive achievements, Dr. Dubinett remains a superb mentor for young scientists, many of whom have become independent and productive scientists in their own right.



Looking back at his association with TRDRP, Dr. Dubinett recalls, "The UCLA Lung Cancer Research Program has substantially benefited from the support from the Tobacco-Related Disease Research Program. Members of our program have obtained awards including Min Huang, Sherven Sharma, Jenny Mao, Marina Stolina, and Kostyantyn Krysan. This

funding has been utilized both for career development and to investigate basic and translational mechanisms in lung cancer. TRDRP funding has been critical in the development of major NIH funding including the National Cancer Institute's Specialized Program of Research Excellence (SPORE) in Lung Cancer awarded to UCLA in 2000. This research encompasses a multidisciplinary team investigating areas of molecular epidemiology, targeted therapies, angiogenesis, and chemoprevention for lung cancer.

As Steve remarks, "The development of a productive, multidisciplinary, nationally recognized program in lung cancer research would not have been possible without support from the TRDRP."



**Hryar S. Karagueuzian, Ph.D.**, senior scientist at Cedars-Sinai Medical Center and professor in UCLA School of Medicine has spearheaded studies on nicotine and cardiac vulnerability to fibrillation that have been continuously funded by TRDRP during the last 10 years. Dr. Karagueuzian has made significant contributions in understanding the mechanisms and control of atrial and ventricular fibrillation, the leading cause of sudden cardiac death in the United States. Karagueuzian and his colleagues recently made a major discovery by demonstrating that chronic nicotine administration in diseased hearts promotes atrial fibrosis and atrial flutter, a kind of rapid atrial rhythm that considerably increases the risk of stroke and sudden death. This work, published in the January 2005 issue of the *American Journal of Physiology: Heart and Circulatory Physiology* received worldwide press coverage. "Although there were anecdotal reports, the reaction between nicotine and disease in promoting cardiac arrhythmias, this hypothesis had not been previously tested systematically," says Hryar Karagueuzian. He further says, "TRDRP funding over the years allowed us to pursue the

mechanisms of action of chronic nicotine exposure and discover an intense increase in atrial tissue fibrosis, a major risk factor for cardiac arrhythmias." Based on the TRDRP-funded research, a new horizon for arrhythmia research has opened in Karagueuzian's laboratory. Dr. Karagueuzian has published over 400 research papers with nearly 50 papers on nicotine and arrhythmias resulting from TRDRP-funded research that helped win additional major research grants from the National Institutes of Health (including SCOR and Program Project), the American Heart Association, and TRDRP.

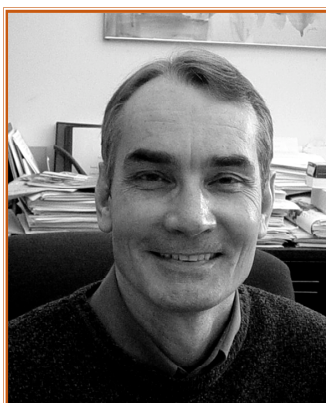
About the future of tobacco's unabated impact on human health, Hryar Karagueuzian says, "As evidence on the potential harms of tobacco use accumulates, 25% of Americans still continue to smoke. A major future challenge is to break the myth of the enduring legacy of fearful yet defiant attitude towards smoking in the USA. While it will be presumptuous to expect a tobacco-free society, advances made in tobacco-related science is an important step to sway the pendulum from smokers' defiance to quitting to their better understanding of smoking-related health risks."

**Hope Landrine, Ph.D.**, is indeed one of the leading African American tobacco researchers in the country today, and TRDRP has had the privilege to fund her work over the last 12 years. Starting in 1993, Dr. Landrine received a post-doctoral training award from TRDRP. Since then, she has been the principal investigator on five TRDRP grants and co-principal investigator on three additional grants. Just this year when a scientific review session demanded that an applicant find a California-based African American tobacco researcher to be a co-principal investigator on a grant to investigate smoking rates and the African American church, the applicant and TRDRP turned to Dr. Landrine. Tackling the thorny questions of the role of acculturation, discrimination, and residential racial segregation in relation to African American smoking, Dr. Landrine has been the lead author or co-author on over 80 peer-reviewed publications, nearly 30 of them a direct result of her TRDRP-funded awards. Dr. Landrine's research has shown that single cigarette sales ("loosies") are commonplace in California's African American communities. Additionally, research lead by Dr. Landrine established that convenience-store clerks sell tobacco products more readily to underage Latino and African American youth than to their white counterparts. Moreover, it was Dr. Landrine who documented that among African American adults, heightened perceptions of racial discrimination were predictive of tobacco use. As a trained clinical and health psychologist, she is currently a research scientist and adjunct professor at San Diego State University, Department of Psychology, where she conducts cancer- and tobacco-research and mentors a new cadre of ethnic-minority cancer- and tobacco-control researchers. Hope says, "I am grateful that TRDRP has continued to support my research. I grew up with TRDRP—from post-doc to professor—and I have been nurtured by the program, all along the way."



## Outstanding

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**Kent E. Pinkerton, Ph.D.**, professor of anatomy, physiology and cell biology, and director, Center for Health and the Environment, University of California, Davis, has made stellar contributions to understanding the effects of environmental tobacco smoke (ETS) on lungs, since receiving his first TRDRP grant in 1990. This and subsequent support from TRDRP enabled Dr. Pinkerton to establish a smoke inhalation facility at UC Davis, which is also used by many scientists from California and elsewhere for their studies. Dr. Pinkerton says, “TRDRP funding allowed us to explore the impact of ETS on lung growth and function. We pursued studies to examine the effects of ETS on the maturation of airway epithelial cells with an emphasis on Clara cells of the distal conducting airways. We also examined the effects of ETS on fetal development and found the immediate impact of ETS to significantly alter the normal metabolic profile of the lungs as early as the first day of life. We also observed alterations in the normal developmental pattern of fetal lung cells due to maternal exposure to ETS. A striking finding was the development of airway hyper-reactivity or “ticklish airways” due to exposure to ETS during *in utero* and postnatal development that was absent if exposure to ETS was only during the postnatal period. Further studies demonstrated these effects to be due to exposure to ETS during a critical window of exposure covering both fetal and postnatal development, rather than simply being due to the duration of exposure.”

Dr. Pinkerton has published nearly 50 research papers as a result of TRDRP funding alone. Dr. Pinkerton reminisces, “Our research has extended to other species and organ systems to show significant impacts of ETS on the development of the brain and heart as well as significant impacts on the immune and other neurological systems. The unique feature of TRDRP funding has been the opportunity to explore the potential mechanisms in which ETS exerts its toxic effects. I am pleased with the opportunity TRDRP funding has afforded to me to launch a research career in neonatal biology and incredible opportunities to establish collaborations with outstanding scientists and collaborators throughout the state of California and the nation.

**Prudence Talbot, Ph.D.**, professor of cell biology, director of Graduate Program in Cell Molecular and Developmental Biology, and a member of Environmental Toxicology Graduate Program at University of California, Riverside, is one of the most recognized scientists whose groundbreaking research has demonstrated how mainstream and sidestream tobacco-smoke exposure affects reproduction in females. Numerous epidemiological studies have shown that smoking can increase the risk of reproductive problems such as infertility and ectopic pregnancy. Dr. Talbot’s studies on fertility, smoking, and early mammalian development, continuously funded through three Research Grant awards by TRDRP since 1995, showed that inhalation of mainstream or sidestream smoke inhibited contraction of oviductal smooth muscles and decreased the rate of transport of preimplantation embryos through the oviduct. Talbot and colleagues developed several new biological assays to simultaneously measure different biological processes that are important in reproduction, as well as other physiological processes. Dr. Talbot’s team found that in some assays, chemicals in sidestream smoke were more inhibitory than mainstream smoke. From amongst more than 5,000 chemicals found in tobacco smoke, Talbot group has already identified at least 40 compounds that have deleterious effects on oviductal physiology at as low as nano- or picogram/mL concentrations.



Dr. Talbot says, “TRDRP funding opened up a new research avenue for my lab and enabled us to examine how both active and passive smoking affect reproduction. From this work, we have gained a better appreciation for how widespread the effects of smoke are on organs of the body, and our work reinforces the conclusion of the surgeon general in 2004 that every organ in the body is a target of cigarette smoke. We now have a greater appreciation for how little we actually know about the numerous chemicals in smoke and how they affect various biological processes. Just as we begin to understand more, we realize there is still much more to be learned about the health consequences of smoking.”



## Doll

*Continued from page 5*

spread of the cigarette habit . . . had so dulled the collective sense that tobacco might be a threat to health that the possibility that it might be the culprit was given only scant attention.<sup>77</sup> Sir Richard's first thought was that lung cancer was somehow related to driving or car-related phenomena such as engine emissions or the tar used to pave the miles of highways that had sprouted over Britain since the turn of the century.<sup>8</sup> But Doll and Hill soon found that only two of the 649 lung cancer cases they examined were nonsmokers. The results were so unexpected at the time that caution prevailed and they were published only as a "Preliminary Report" in the September 1950 issue of the *British Medical Journal*.<sup>9</sup> This paper was actually not the first peer-reviewed article to note an epidemiological link between smoking and lung cancer: just a few months prior to Doll and Hill's article, a similar report by Wynder and Graham had appeared in *JAMA*.<sup>10</sup> However, it was Doll's next study that proved to be definitive.

Displaying the scientific diligence that would mark his entire career, Sir Richard followed up his initial finding with a study that utilized a sample consisting of every doctor in the UK (a sample size of 34,439) and that showed prospective mortality over 20 years.<sup>11</sup> It was this study, published in 1954, again with Hill, that would be a veritable "coffin nail" for the tobacco industry itself. The results were so alarming and so compelling that the British health minister called a press conference to announce that the link between smoking and lung cancer should be considered definitive. Almost everyone in the room was smoking, including the health minister himself, who was a chain smoker at the time.<sup>8</sup> The study was a stunning achievement, one (it should be remembered) that was accomplished at a time when computers and programmers were available only to the military.\*

Damning though the results were, public acceptance was slow in both Britain and the United States. It was not until 1964 that the U.S. surgeon general's first report on the dangers of smoking appeared. The tobacco industry, of course, shifted into high gear almost immediately and began its by now infamous campaign to obscure the scientific evidence, deny the facts, and market so-called "safe" cigarettes—profit, as always, trumping prudence as well as science.<sup>13</sup>

Unfortunately, it was too late for many victims of the tobacco industry's relentless campaign to promote cigarette smoking. Watson and Crick's "Molecular Structure of Nucleic Acid" had just appeared in *Nature* the year before Doll and Hill's 1954 landmark. Elucidation of the biological basis and thus the development of effective treatments for

lung cancer would have to wait. The insight that lung cancer proceeds from the inactivation of multiple tumor suppressor genes would take several more decades, beginning with the identification of p53 mutations in 1989.<sup>14\*\*</sup>

Sir Richard went on to publish hundreds of papers on environmental risk factors and disease, including studies of oral contraceptives, alcohol consumption, electrical power lines, radiation, and aspirin's protective effect on heart disease. And he and his colleagues, most notably Richard Peto, in an undertaking of relentless scientific perseverance, continued to study the link between smoking and disease by following for the next 50 years the same group of doctors who were the subjects of Doll's 1954 analysis. They went on to show that smoking might cause other diseases besides lung cancer and that prolonged cigarette smoking from an early age had a much greater effect than originally suspected.<sup>1</sup>

***"Posterity may regard the epidemiology of non-communicable diseases as Britain's most important contribution to medical science in the second half of the 20th century. If so, then Richard Doll's name will come first to mind."<sup>215</sup>***

### A conceptual upheaval

Doll and Hill's work resulted in a paradigm shift of epic proportions that went well beyond the demonstrated relationship between smoking and lung cancer. Not only did they show that something as ubiquitous and apparently innocuous as smoking was harmful to health (thus opening the door to the study of environmental toxicology), but their work also introduced the startling notion that what was then thought to be voluntary behavior (now known as "lifestyle choices") could influence the propensity to contract disease. Up to that point, disease was considered to be due primarily to microorganismal invasion and epidemiology had been largely confined to the study of infectious disease. It is difficult in this day and age to imagine the revolutionary implications of this concept. As the *Times Online* put it: "Posterity may regard the epidemiology of non-communicable diseases as Britain's most important contribution to medical science in the second half of the 20th century. If so, then Richard Doll's name will come first to mind."<sup>15</sup> These ideas were the precursors of the health-related social-behavioral sciences and social epidemiology that we know today and which have become an integral part of the TRDRP

\*Flexible computing in public health did not begin until 1976, when CDC epidemiologists first employed a refrigerator-sized machine running a FOR-TRAN program called Socrates.<sup>12</sup>

\*\*The complexity of the molecular events underlying lung cancer initiation and promotion, coupled with the fact that the entire airway is exposed to a complex carcinogenic insult in the form of tobacco smoke, have made lung cancer stubbornly resistant to a cure. However, recent advances in detection, genetic susceptibilities, and therapeutics, some of which have been pioneered and developed by TRDRP-funded lung cancer researchers,<sup>13</sup> have lent renewed impetus to a field that has historically been one of the most depressing for health care providers and their patients. There is light at the end of this tunnel, but we have some way to go yet.

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## Doll

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smoking-related disease portfolio.

Doll and Hill's work with smoking and lung cancer had implications beyond the extension of epidemiology to the study of non-communicable disease. The rigorous mathematical methodologies they applied to the study of disease in human populations conferred a degree of legitimacy on epidemiology that had largely eluded it up until then. Doll and Hill also introduced the term "prospective study" in their 1954 landmark paper and thus contributed in a concrete way to the development of epidemiological methodology.<sup>16</sup>

Sir Richard's influence on public health went beyond the conceptual and methodological underpinnings of epidemiology, however. At the same time that he began to study lung cancer, he and like-minded colleagues began to recognize that socioeconomic status and health were closely related, and that political decisions applied to poverty could have profound public health implications. Sir Richard played a role in this nascent movement as a founding member of the Society for Social Medicine, a group of British physicians who were proponents of this viewpoint.<sup>17</sup> The introduction into the public psyche of the concept that government policy could affect public health very likely set the stage for the future political movements that led to California's Proposition 99 and the passage of AB 13, which prohibits smoking in the workplace, bars, and gaming clubs.

Sir Richard received over 20 prizes and awards for his work, including the U.N. Award for Cancer Research in 1962 and, with Richard Peto, the King Faisal International Prize in medicine for their work on tobacco-related disease. Some of the sturdiest scientific underpinnings of the WHO's Framework Convention on Tobacco Control, now with over 100 country signatories, are Sir Richard's work; he was always a strong advocate of the convention.<sup>18</sup> He was the recipient of honorary degrees from 13 universities. In 2004, he participated in a celebration marking the structural completion of the Richard Doll Building at Oxford University. It will house some of the U.K.'s top cancer researchers, a fitting tribute to the man who started it all.

In 1997, Richard Doll told an interviewer for the British Medical Journal that his most heartfelt wish for the new millennium was "... to see it."<sup>19</sup> Sir Richard not only lived to see the new millennium; by saving so many lives, he enabled many others to see it too. He and his colleagues contributed concepts to tobacco-related disease research that will be influential for many years to come. TRDRP salutes Sir Richard Doll, his life, and his work. As we continue our ongoing fight against tobacco-related disease into the next millennium, we all stand on his shoulders. Fortunately for us, this gracious gentleman, distinguished scholar, and public health advocate was also a true scientific giant; because of him, we see much further.

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## TRDRP

*Continued from page 3*

tion and the surface adsorption properties of tobacco smoke. Greatly improved measurement tools for this were being developed in California. Also, there were TRDRP-funded economic and legal studies supporting policies for smoke-free environments including public spaces, and more recently, residential rental properties.

### Building research capacity

TRDRP funding has been a bold investment in California's research infrastructure and knowledge base. More scientists, laboratories, and academic institutions are now focused on tobacco-related studies than would have been if TRDRP did not exist. This is the very momentum and effort that voters supported in passing the groundbreaking anti-tobacco initiative, Proposition 99. By focusing resources, TRDRP was generating the research that directly benefited smokers, ex-smokers, and nonsmokers alike. Many centers of excellence, for example, the University of Southern California, the Scripps Research Institute, and the University of California campuses at Davis, San Francisco, San Diego, Los Angeles and Irvine grew with the aid of TRDRP funding. Both UC Irvine and USC were designated as two of the original National Cancer Institute-funded Transdisciplinary Tobacco-Use Research Centers (TTURC) in the nation, following initial TRDRP funding. Also, after some of the original funding of key lung cancer researchers at UCLA by TRDRP, the UCLA Jonsson Comprehensive Cancer Center was designated as one of only six NCI-funded Specialized Programs of Research Excellence in Lung Cancer (SPORE).

This is all a boon to California as well as an economic generator of jobs and a means to leverage even more federal and other foundation research dollars into the state. TRDRP career development grants (new investigators, post-doctoral awards, and dissertation support) have built a cadre of talented young and new scientists over the years whose careers are now specialized in the field of tobacco-related disease research. Many today are either nationally or world recognized in their field. Taking advantage of this development, TRDRP is demonstrating foresight and initiative in creating the Cornelius Hopper Diversity Award Supplement. This award is designed to have senior scientists mentor trainees who are from and/or committed to underrepresented communities where tobacco-related health disparities exist and bring them into the tobacco-research field.

From this TRDRP focus has evolved national leadership in tobacco-related disease research funding. TRDRP actively collaborates with federal agencies and other significant funding and scientific organizations. The innovative funding of high-risk, high-gain IDEA awards originated by TRDRP has now become the R21 mechanism used by the NIH. TRDRP has been the model and advisor for other state pro-

grams attempting to accomplish the same goals, notably the states of Minnesota, Florida, and Colorado—until the Colorado legislature eliminated funding and shut down their program.

### Looking forward

Despite this history of achievements, TRDRP is still not without threats to its mission. The state continues to divert one-fourth of the Proposition 99 Research Account funds to support the California Cancer Registry. In 2005, this deprived TRDRP of over \$5 million that could have been used for research grants. Obviously, success remains no assurance of security from political maneuvering in an atmosphere of constrained resources. Diminishing TRDRP and the mandate of Proposition 99 only plays further into the hands of a pro-tobacco industry agenda.

Building on 15 years of research progress in the fight against tobacco, TRDRP looks to the future to continue to be a leader, to be innovative, and to make further advances in scientific areas important to California. The program's mission is clear: like a finely polished lens, focus research dollars for the prevention and treatment of tobacco-related diseases; strategically fund studies in economics, policy, community intervention, and cessation methods; and aggressively disseminate research findings at local and state policy levels ultimately working toward a smoke-free and healthier society.

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## NEW THIS FALL

### **TRDRP INTRODUCES:**

### ***On-line Application Submission for 15th Cycle***

***Applications can only be submitted  
on line at [www.trdrp.org](http://www.trdrp.org)***

***On-line submission closes at 11:59 pm PST  
Thursday, January 19, 2006***

***Paper applications will no longer be accepted!***