

**The Virginia Youth Tobacco Project  
of Virginia Commonwealth University**

**Semi-Annual Report to  
The Virginia Tobacco Settlement Foundation**

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**The Virginia Youth Tobacco Project  
of Virginia Commonwealth University  
Report to the Virginia Tobacco Settlement Foundation  
— Executive Summary —**

The money provided to the Virginia Youth Tobacco Project (VYTP) by the Virginia Tobacco Settlement Foundation (VTSF) is making possible the coalescence of a first-rate research program in the Commonwealth of Virginia, an effort that is now coming to grips with and will ultimately provide solutions for the problem of youth tobacco use. VTSF's funding is working to build the capacity of Virginia universities to attract world-class faculty and the most promising students, and it will leverage significant institutional support from the federal government and private foundations. In so doing, VTSF is enabling the extension and integration of our tobacco-research effort, and encouraging a concerted focus on the critical issue of youth tobacco use and addiction. It is also reinforcing the local and regional support that the Commonwealth's universities provide for public health and the economy, even as it works to establish the national and international reputation of Virginia as the home of first-class tobacco-use-prevention research and evaluation.

The practical result of these efforts will be the generation of a wide and well-founded array of intervention options for a broad spectrum of people and their tobacco-related needs – pharmacologic treatment, motivational assistance, carefully evaluated community and school-based education programs. These will provide for new and better use-prevention interventions, based on a surer knowledge of why and how young people form the tobacco habit.

In pursuit of these desirable results, the VYTP has established the four overarching goals listed below to guide our efforts. The attached report articulates the research and evaluation programs that are now leading us toward their attainment. It also briefly discusses upcoming challenges for the project, and plans to address those challenges with action in the months ahead.

Goal 1. Identify groups and individuals especially vulnerable to tobacco-use initiation and nicotine addiction, and understand the biological factors that mediate that vulnerability.

Goal 2. Determine better, more reliable ways to prevent the progression of young people from occasional tobacco use to nicotine addiction.

Goal 3. Apply the best scientific techniques to the evaluation of school- and community-based youth tobacco-use-prevention initiatives, and thereby facilitate improvements in the efficacy, reliability, and cost-effectiveness of these programs.

Goal 4. Make available to policy makers the latest and best empirical information on the social and economic costs of tobacco and on the prospects for public gain from a variety of tobacco-control strategies.

# The Virginia Youth Tobacco Project of Virginia Commonwealth University

## Semi-Annual Report to The Virginia Tobacco Settlement Foundation

According to the federal government's Centers for Disease Control and Prevention, tobacco use in the United States results in approximately 440,000 deaths per year.<sup>\*</sup> This is a greater toll in human life than that exacted by car accidents, murders, suicides, drug and alcohol use, and HIV/AIDS, combined. In monetary terms, tobacco use leads to over \$75 billion in public and private health-care costs each year, and reduces the productivity of Americans by more than \$80 billion per year. If current trends go unchecked, American taxpayers will have to contribute, every year, more than \$30 billion – an average of some \$300 per household – to deal with the devastation wrought on our nation's health by tobacco; and more than 6 million people now under the age of 18 will die from tobacco's effects.<sup>†</sup> In Virginia alone, people spend yearly more than \$1.6 billion on tobacco-use-related health care, and over 9,000 Virginians die each year from tobacco-use-related illnesses.<sup>‡</sup>

Once people form the tobacco habit, they usually find it extremely difficult to quit — because the nicotine that tobacco delivers to the body is one of the most addictive substances known. So, to curtail tobacco's enormous and tragic burden on our public health and welfare it is essential that we find more reliable ways to help people kick the habit, and more importantly, to prevent young people from becoming tobacco users in the first place.

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<sup>\*</sup> Total mortality and economic cost figures reported in *Morbidity and Mortality Weekly Report* (MMWR) 51(14): 300-3 (April 12, 2002) <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5114a2.htm> Data cited are based on annual estimates for the years 1995-1999. For details on tobacco-attributable diseases and economic costs, see <http://apps.nccd.cdc.gov/sammecl/>

<sup>†</sup> Federal and state per-capita tax burden based on data from *MMWR* 43(26): 469-72 (July 8, 1994) <http://www.cdc.gov/mmwr/PDF/wk/mm4326.pdf> For projected mortality, see Centers for Disease Control and Prevention, *Tobacco Control State Highlights 2002: Impact and Opportunity*, Atlanta, GA: Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office of Smoking and Health, 2002, [http://www.cdc.gov/tobacco/statehi/html\\_2002/FrontMaterial.htm](http://www.cdc.gov/tobacco/statehi/html_2002/FrontMaterial.htm)

<sup>‡</sup> Centers for Disease Control and Prevention, *Tobacco Control State Highlights 2002*, [http://www.cdc.gov/tobacco/statehi/html\\_2002/virginia.htm](http://www.cdc.gov/tobacco/statehi/html_2002/virginia.htm)

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## **Goal 1. Identify groups and individuals especially vulnerable to tobacco-use initiation and nicotine addiction, and understand the biological factors that mediate that vulnerability.**

Large-scale, population-based twin studies have documented genetic influence over tobacco-use behavior and nicotine dependency – both the propensity to initiate tobacco use, and the probability of addiction. As specific genes are identified, prevention initiatives may be better targeted. And as we achieve more precise knowledge of the biological and behavioral processes that these genes regulate, more reliable and potent pharmaceuticals can be produced. As well, a number of studies have found that young people are more sensitive than adults to the physiological and behavioral effects of nicotine. Understanding the parameters and mechanisms of these differential sensitivities is an important goal of research, and will provide the foundation for much more effective youth-intervention initiatives.

### **Research questions being asked and activities being conducted by VYTP in pursuit of this goal.**

#### **1. A. What genes are reliably associated with nicotine addiction, and how do these genes interact with environmental factors to influence tobacco use and the progression to dependency?**

VYTP researchers at the Virginia Institute for Psychiatric and Behavioral Genetics at VCU, under the direction of Dr. Kenneth Kendler, have been studying members of the Mid-Atlantic Twin Registry, which was established by VCU researchers in 1978, to understand the relative contribution of genetic inheritance to the incidence of tobacco use and dependency. Dr. Kendler and his colleagues have state-of-the-art molecular genetics facilities and extensive experience in analyzing the connection between genotypes and health-related behaviors. They have developed statistical models to determine whether there are genetic vulnerabilities specific to nicotine, or whether such vulnerabilities are more complexly related to other drug-abuse vulnerabilities or psychosocial characteristics. For example, they recently determined that environmental (non-genetic) risk factors are more highly correlated to the use of non-smoked tobacco products than to the use of smoking tobacco. They also have made strides in understanding an array of factors that influence the initiation of tobacco use, progression to regular use, and the development of nicotine addiction.

Dr. Donna Miles of VCU's Department of Human Genetics and her colleague Dr. Roy Pickens of VCU's Department of Psychiatry are also studying

the relative influence of genes and environment on the progression of adolescents from experimentation with tobacco to nicotine addiction. They are conducting a follow-up of 1412 Virginia twin pairs who were interviewed regarding their tobacco use in the years 1990-1992, when they were age 8-16. This work will produce valuable longitudinal data showing the rates at which different types of adolescents progress to nicotine dependency, it will facilitate investigation of gender and age variables in tobacco-use patterns, and it will help increase our understanding of the influence of protective factors, such as parental monitoring, on the development of tobacco addiction. Most importantly, information produced in this work should help determine whether, and the extent to which, different genes influence each of the various stages of the youth tobacco experience – initiation, regular use, development of dependency, and the ability to quit. As we understand better why some young people initiate tobacco use and others don't, why some become frequent users and others don't, why some become highly dependent and other don't, and why some can quit and others can't, we will be able to design and target prevention interventions that are more precisely tailored to individuals in their actual tobacco-use situations.

### **1. B. What gene groups are reliably implicated in nicotine dependence?**

Dr. Kendler and his colleagues are also studying patterns of gene linkages, in sample populations drawn in Richmond, Virginia and Christchurch, New Zealand, to determine the relationship of these gene groups to tobacco use and nicotine addiction. The study of gene groups can guide the search for candidate genes, and thus provide important insights into the basic physiological mechanisms by which vulnerability to tobacco is mediated. Working with Dr. Kendler, VCU's Dr. Xiangning Chen has identified a group on chromosome 2 of considerable interest respecting the metabolism of nicotine, and has followed up this preliminary, twin-based work by developing a homologue gene model in mice. Using experimental animals permits much more detailed biological investigation of the genetics of tobacco use and nicotine addiction; and in most of the cases thus far studied, researchers have found homologous genes in humans and mice governing the uptake and metabolism of nicotine. Thus, work of this kind can lead to more precise characterization of the neurophysiological and behavioral significance of candidate genes. For example, are they associated with known reward-producing or anxiety-reducing brain systems?

### **1. C. What specific genes are activated by acute nicotine-dose challenge?**

Starting from the premise that an animal's measurable physiological and behavioral sensitivity to a dose of nicotine indicates a vulnerability to addiction, VYTP researchers in VCU's Institute for Drug and Alcohol Studies and its Department of Pharmacology and Toxicology have, under the leadership of Dr.

Billy Martin, initiated a project to identify the mouse genes that are activated as a result of nicotine administration. Dr. Imad Damaj and Dr. Michael Miles, in collaboration with Dr. Chen, have begun the examination of some 12,000 candidate genes. With their screening techniques they have already identified 10 genes that warrant additional investigation. One in particular encodes an enzyme that is important in memory regulation and is known to be altered in alcohol-dependent animals.

VTSF funding has been crucial in facilitating new collaborations at Virginia universities, such as those between professors Martin and Kendler. The success their teams have so far realized together has encouraged them to submit a joint, multi-million-dollar center-grant proposal to the National Institutes of Health to further their research – to bring, right here in Virginia, cutting-edge genetic epidemiology into synergy with first-rate laboratory pharmacology. We can expect that the findings of this research will produce a base of knowledge on which to build a new generation of tobacco-use-prevention strategies and treatments. Moreover, collaborations such as this, advanced with VTSF funding, will make possible the education of the next generation of tobacco-research scientists – our best hope for comprehensive solutions to the complex public-health problems attributable to tobacco use.

#### **1. D. Are juveniles more sensitive than adults to acute doses of nicotine, and therefore more vulnerable to addiction?**

VYTP researchers working with Dr. Martin, including Dr. Joe Ritter of the Department of Pharmacology and Toxicology and Dr. Richard Glennon of VCU's Department of Medicinal Chemistry, are testing groups of juvenile and adult mice to determine each age group's specific routes and rates of metabolism of nicotine, their specific sensitivity to acute doses of nicotine and synthetic analogues of nicotine, and their degree of drug dependence that develops with repeated administration of nicotine and synthetic analogues. In conjunction with this work, VYTP researchers are also comparing groups of juvenile and adult mice that have been genetically engineered to lack certain known nicotine brain receptors. These investigations, which also are benefiting from an extra-VCU collaboration with medicinal chemist Dr. F.I. Carroll of North Carolina's Research Triangle Park, will increase our knowledge of the pharmacology of nicotine and related compounds, and may lead to promising medicinal treatments to block the craving for nicotine that keeps young people using tobacco. Related research by Dr. Martin and his colleagues has already shown that Bupropion, an antidepressant now being prescribed to help people quit smoking, owes its nicotine anti-addictive properties to a metabolite of the medicine. Findings of this sort have in the past led to pharmaceutical treatments that are more reliable and potent, with fewer side effects.

Researchers at George Mason University, under the direction of Dr. Robert Smith of GMU's Department of Psychology, affiliated with VYTP through VTSF's Virginia Research Consortium, are also investigating nicotine's effects on biological and behavioral processes in young animals. They too are studying nicotine's effect on gene activation, and their research is looking specifically for persistent cognitive changes that occur in young rats exposed to nicotine. As well, Dr. Smith and his colleagues are investigating the extent to which juvenile exposure to nicotine increases animals' propensity to self-administer cocaine.

Parallel work such as this that is proceeding at GMU and VCU amplifies the ability of science to produce reliable and useable results. Coordinating related research in affiliated institutions, as VTSF is doing through its consortium of Virginia universities, promises to foster a critical mass of scientific talent that will put Virginia at the forefront of tobacco research.

### **1. E. How does exposure to nicotine early in life influence the propensity to become addicted to this substance?**

People use substances like tobacco, and some become addicted to nicotine, because these things produce pleasurable effects or other perceived benefits when they are used – that is, substance use is “reinforced” by subjective effects. Dr. Martin and his colleagues at VCU are making use of two techniques to assess the subjective, reinforcing properties of nicotine and related compounds. Given the proper conditions, many animal species will self-administer nicotine – as they will most of the drugs that are abused by humans. Dr. Jenny Wiley, an associate professor in Dr. Martin's department, is developing laboratory methods to study nicotine self-administration behavior among juvenile and adult mice. An alternative to the study of self-administration behavior is the so-called “conditioned place preference” experiment. Here, an animal is conditioned to associate certain environmental cues with the effects of a dose of a drug; and a drug with reinforcing properties will reliably induce an animal so conditioned to seek out the environment with those cues. Dr. Sherry Grabus, a post-doctoral research fellow in VCU's Department of Pharmacology and Toxicology, is conducting nicotine place-preference experiments. Findings from this research will allow precise study of behavioral conditions and processes that lead from first exposure to nicotine to nicotine dependence. As well, this will permit laboratory study of compounds that may disrupt the transition in youths from occasional tobacco use to daily nicotine dependency.

## **Goal 2. Determine better, more reliable ways to prevent the progression of young people from occasional tobacco use to nicotine addiction.**

There is now solid, scientific evidence that a large proportion of the users of tobacco continue to take this substance because they are nicotine dependent; and it is also clear that nicotine is more addictive than most illicit drugs. Thus, once people become dependent, their chances of quitting, given current treatment options, are remarkably low. That's because tobacco is so readily available in our society, and because the craving for tobacco – the subjective experience of unpleasant effects from nicotine withdrawal – strongly reinforces continued acquisition and use. Unfortunately, surveys suggest that three-quarters or more of America's youth try tobacco at least once by the time they are 18 years of age. Therefore, VYTP researchers are convinced that a key to reducing the public-health effects of tobacco use lies in prevention interventions that target young tobacco users before they become highly nicotine dependent.

### **Research questions being asked and activities being conducted by VYTP in pursuit of this goal .**

#### **2. A. What are the actual patterns (use frequency and puff topography) of cigarette smoking behavior among adolescent individuals, and what relationship does smoking pattern have to genetic, physiological, and psychosocial characteristics of these individuals and to the development of nicotine dependency?**

VYPT researchers in VCU's Clinical Behavioral Pharmacology Laboratory, led by Dr. Thomas Eissenberg of VCU's Department of Psychology, have developed techniques to safely and ethically study the smoking behavior and associated characteristics of adolescent smokers. With scrupulous procedural regard respecting informed consent by both the adolescents involved and their parents, Dr Eissenberg's team is now in the process of recruiting subjects for a series of path-breaking experiments that will shed new light on the crucial interval between tobacco-use initiation and nicotine addiction in young people. Subjects for recruitment are persons 12-18 years of age who are current cigarette smokers but not yet highly addicted – that is, they smoke at least one cigarette per week, but not more than an average of ten cigarettes per day. Previous research has determined that people below the ten-cigarettes-per-day threshold are at most mildly nicotine dependent. In the clinical evaluation, subjects will be administered a set of questionnaires, which have been developed and standardized to ascertain demographic, psychological, personality, behavioral, and familial characteristics of adolescents, and to quantify the subjective effects

of nicotine administration and withdrawal. In the typical evaluation protocol, subjects will arrive in the laboratory in the morning, answer the questionnaires, smoke a cigarette (their own, or one provided for them) through a device that records puff topography, have measurements taken of their heart rate, breath carbon monoxide level, levels of saliva cotinine (a metabolite of nicotine) and cortisol (a stress-related hormone), and answer the nicotine effects and withdrawal questions again. Researchers will conduct follow-up assessments of each subject, by telephone one month, three months, and nine months, after the initial laboratory session, and in person six months and one year after initial testing. Dr. Eissenberg is also planning to do a series of collaborative experiments with Dr. Kendler's and Dr. Martin's teams to test specific gene activation effects in his research subjects.

Results of these clinical-laboratory and related experiments will provide a precise picture of adolescent smoking behavior, and permit researchers to understand how smoking is associated with a wide range of individual characteristics. Collecting these facts is an essential first step in understanding how tobacco use becomes part of adolescent life, and how that process might be disrupted by targeted prevention interventions.

## **2. B. How can our knowledge about youth smoking behavior be put to work to help in the design of interventions that prevent young people from succumbing to nicotine addiction?**

In conjunction with the clinical-laboratory procedures described above, and using funds provided through VYTP, researchers with VCU's medical college in its Division of Addiction Medicine and Psychiatry, working under the supervision of Dr. Deborah Haller, will perform assessments of a number of dependence-prevention interventions. Dr. Michelle Acosta, a post-doctoral fellow, has begun the study of a very promising type of intervention, motivational interviewing, which provides the subject with both general and personalized information about the consequences of smoking, including feedback on the physiological and psychological results measured in the clinical-laboratory evaluation. These interviews will be audio taped, and some sessions will be selected for preservation (given the informed consent of subjects and their parents to do so) to provide a valuable evaluation and teaching tool for future intervention activities. Researchers will also test various media-based educational/informational interventions to determine their relative efficacy in curtailing smoking behavior. Once this experimental paradigm is firmly established, VYTP researchers will be able to assess new intervention programs as they become available, making possible a highly reliable approach to tobacco-use-prevention design and evaluation.

## **2. C. How can our knowledge of the special risks that some groups of young people face be used to improve use-prevention interventions and reduce the public-health burden of tobacco?**

Young people who have been diagnosed with attention-deficit / hyperactivity disorder (ADHD) smoke at rates approximately twice that of others of similar age. With funding provided by the Virginia Research Consortium, Dr. Steven Evans and his colleagues in James Madison University's Tobacco Prevention Research Center, in collaboration with local public schools and a pediatric clinic in Harrisonburg, are designing and testing a tobacco-use-prevention intervention strategy that incorporates both psychosocial and pharmacological techniques to tailor treatments specifically for this vulnerable group of youngsters. This research offers an excellent example of how VTSF funding is producing opportunities for Virginia's universities to have a direct, beneficial impact on public health in the Commonwealth.

Also at JMU, researchers are investigating adolescents' propensity to use tobacco consumption as a weight-management strategy. Dr. Monica Reis-Bergen is creating assessment tools to study attitudes and beliefs related to this particular tobacco-use motivation, to make possible the identification and targeted treatment of young people so inclined.

Although morbidity and mortality rates attributable to tobacco use are generally higher among men than women, adolescent females represent a group particularly vulnerable to the future ill effects of tobacco dependency, because of the health impact on the unborn children of women who smoke and are too addicted to quit. VYTP-affiliated, consortium-sponsored researchers, under the leadership of Dr. Peggy Meszaros of Virginia Tech's Department of Human Development, are studying psychosocial risk factors and tobacco-use-prevention strategies among adolescent females. In conjunction with this research, investigators are conducting inquiries into neurological and behavioral correlates of tobacco use, and the role of bitter-taste sensitivity as a protective, anti-tobacco-use factor.

Again, it is important to stress the value of the research coordination that is being made possible at Virginia universities by VTSF's consortium. Through this mechanism we are constructing a state-wide, transdisciplinary "institute without walls," within which university research administrators, faculty senior and junior scientists, and promising students from many fields will work together on an integrated program of basic and applied research to attack the complex problem of youth tobacco use. We are at the beginning of a process of investment in collaborative strategic planning that is likely to pay enormous dividends in the public health and welfare of Virginians – and benefit young people around the world who are at risk from the brutal effects of tobacco use.

**Goal 3. Apply the best scientific techniques to the evaluation of school- and community-based youth tobacco-use-prevention initiatives, and thereby facilitate improvements in the efficacy, reliability, and cost-effectiveness of these programs.**

While states and localities around the country vary a great deal in the resources they are devoting to school- and community-based prevention programs, some are spending considerable funds and supporting a wide variety of initiatives. Moreover, the Centers for Disease Control and Prevention are calling for major increases in funding for these programs, considering “best practices” in this realm to be crucial to a comprehensive, national tobacco-control strategy. Given the level of current and projected investment and the public-health stakes involved, it is imperative that our youth-outreach programs are carefully tested, and that a comprehensive testing program be put in place as an integral component of these efforts to curtail youth tobacco use. VYTP has established and deployed an evaluation team – the Youth Tobacco Evaluation Project (YTEP) – to assure that the Commonwealth’s prevention investment, through VTSP, is well used and produces detailed and reliable evidence of effective results.

**Research questions being asked and activities being conducted by VYTP in pursuit of this goal**

**3. A. What kinds of evaluation methodologies are needed and appropriate for VTSP-funded school- and community-based programs?**

All the school- and community-based programs the VTSP has funded have been selected based on a thorough review of provider-organization capability and program design, and on careful consideration of local and regional community needs. This process resulted in contract awards to a large number of organizations, offering a wide variety of activities, in a range of settings, and targeting numerous types of youth groups.

Faced with this complex array of variables, the YTEP, under the leadership of Dr. Elizabeth Fries of VCU’s Department of Psychology, decided that in order to engage a comprehensive evaluation, several methods must be pursued concurrently, in an integrated fashion. These include: program monitoring, process evaluation, outcome evaluation, and impact evaluation. To effectively monitor the 110 initiatives now funded by VTSP, Dr. Fries and her team – whose senior members include Dr. Ilene Speizer and Dr. Diane Wilson of

VCU's Department of Preventive Medicine and Community Health, Dr. Ramesh Ramakrishnan of VCU's Department of Biostatistics, and Dr. Brian Smith of VCU's Department of Psychology – have developed and deployed assessment tools to track each program's activities and resource usages, to determine if each program is proceeding according to its plans, and to keep records of procedural changes and problems encountered in program implementation. This has prepared the ground for process evaluation, which seeks to determine the suitability of a given program for its intended audience, and the extent to which the audience comprehends programmatic materials and activities. The YTEP team is also well along in the important work of assessing the extent to which program participants are changing with respect to knowledge, attitudes, behaviors, skills, and community norms – that is, evaluating observable outcomes – and the extent to which observed changes can be attributed to elements of the program itself – that is, evaluating program impacts. Considerable pre-testing of program participants has been done to establish a baseline of conditions by which to judge program outcomes and impacts. It is noteworthy that VYTP evaluators are considering outcome and impact evaluations to be appropriate only for programs that serve young people of 6<sup>th</sup>-grade age and above. In the case of younger participants, we are surveying children or their parents to evaluate only the program processes involved.

In this and other matters of evaluation design and implementation, the YTEP team is working closely with VTSF staff and with program providers to make sure that evaluation methods are appropriate to the programs in question and each particular target audience, and that a fair picture of the strengths and weaknesses of each program is produced. A major benefit of the collaboration between evaluators and program providers is the education both sides of the partnership are receiving. YTEP held seven regional day-long training sessions in June-July 2002 to familiarize program providers with evaluation tools, and to allow the people involved to get to know one another. Through these processes of instruction and consultation, program providers have learned valuable social-science-based evaluation techniques that are being applied across many programs. At the same time, VYTP evaluators are gaining a deeper and more nuanced understanding of individual programs. As a result, future school- and community-based efforts at tobacco-use prevention will be more accountable, and potentially much more appropriately designed for a wide array of user needs.

A note on the issue of research involving adolescents: In consultation with VCU's Institutional Review Board, VYTP concluded that instead of seeking pre-survey parental consent, the YTEP would pursue a strategy of providing parental notification that their children would be asked to participate in the evaluation. This was combined with a scheme for coding questionnaires that allows us to keep individual survey respondents anonymous, and yet still measure program outcomes and impacts and correlate demographic and other categorical information on our subjects pre- and post-intervention.

The Virginia Research Consortium is also funding an independent evaluation program, being conducted by researchers Dr. Cheryl Talley and Dr. Charles Lockett of JMU's Department of Psychology. In this effort, researchers are evaluating the efficacy of a comprehensive smoking-cessation program called "Breathing for Life." This program combines techniques of cognitive-behavior therapy, breath training, medical hypnosis, and auricular acupuncture. In general, cessation treatments are notoriously poor at preventing relapse. Combinations of treatment modalities, such as that offered in the "Breathing for Life" program, hold considerable promise; they must be subjected to rigorous, scientific evaluation in order to understand their worth. With VTSF funding, researchers at JMU are proceeding to apply such rigor.

### **3. B. What are we learning from our evaluation efforts that will help us improve the success of our tobacco-use-prevention effort?**

VYTP's evaluation effort through YTEP is producing prodigious amounts of information on VTSF-funded programs and their participants, and the YTEP team is hard at work analyzing the data as it comes in. For the outcomes-evaluation pre-test survey of 6<sup>th</sup>-12<sup>th</sup>-grade-level participants, over 29,000 questionnaires were sent to the programs, and some 4,800 completed forms have been received and analyzed. In addition, over 10,000 process-evaluation surveys have gone out to 4<sup>th</sup>- and 5<sup>th</sup>-grade-level participants, and more than 4,500 surveys to parents of 3<sup>rd</sup>-grade-level and younger participants. In the near term, results of this work will tell us how the funded programs are working and what impacts the programs are having on adolescents' knowledge, attitudes, and behaviors regarding tobacco. In the longer term, after follow-up information is collected, we will be able to say with confidence which programs and program elements have lasting effects on youth tobacco use, and what effects program participation has on family, home, and school environments. As well, results will be fed back to program providers to help them improve program management and planning, and to facilitate the design of new, more effective programs and program elements.

## **Goal 4. Make available to policy makers the latest and best empirical information on the social and economic costs of tobacco and on the prospects for public gain from a variety of tobacco-control strategies.**

The federal Centers for Disease Control and Prevention have put forth information, based on epidemiological investigation, estimating the social cost of tobacco in terms of American public health and welfare, and have advanced guidelines for national, state, and local spending on tobacco-control efforts. In some cases considerable evidence has been accumulated that government spending on tobacco control results in reduced rates of tobacco use, and proportionately favorable reductions in social costs. For example, counter-marketing advertisement programs have shown great promise in terms of cost effectiveness. In other cases – for example, increased spending on enforcement of youth-tobacco-access laws – little in the way of solid data are currently available that connects spending to results. Questions surrounding policy decisions about tobacco are complex and will require careful, sometimes painful, efforts at setting priorities and making necessary tradeoffs. If Virginia policy makers are to make sound, evidence-based decisions about tobacco control, they will need empirical data relevant to a range of policy options and specific to the costs and benefits of government action in and for the Commonwealth.

### **Research questions being asked and activities being conducted by VYTP in pursuit of this goal.**

#### **4. A. What institutional structures are appropriate to organize tobacco-related policy research?**

With funding from the Virginia Research Consortium, researchers at the University of Virginia under the leadership of law professor Dr. Richard Bonnie, are developing advanced capability to collect, analyze, and make available policy-relevant information to guide decision making in Virginia with respect to youth tobacco-use control. They have established the Working Group on Youth-Centered Tobacco Policy Research to plan and coordinate their efforts. This organization will sponsor a bi-weekly tobacco-research colloquium, providing a unique forum for the presentation and discussion of empirical research proposals and findings. As a result of recent discussions, for example, plans are afoot at UVA to employ existing data sets to study the relationship between a variety of tobacco-regulation types and the incidence of low-birthweight babies.

#### **4. B. What opportunities should be pursued in the near term to inform policy making with respect to tobacco control in Virginia?**

Considerable sums are expended by governments and public-service organizations to create and disseminate anti-tobacco advertising. Recognizing the crucial importance of understanding how this spending actually affects behavior, policy researchers at UVA are planning to investigate the connection between specific counter-advertising messages and risk-perception among youth with respect to tobacco. Investigators are particularly interested in the role of incidental positive and negative emotional cues in anti-smoking public-service announcements. Previous findings suggest that positive-affective cues reinforce existing anti-smoking attitudes among youth, while negative cues may encourage the formation of such attitudes. A combination of survey and laboratory techniques will be used to understand the dynamics involved. Findings here can help guide the design of future anti-tobacco media campaigns.

UVA researchers are also planning to work with Dr. Fries and her evaluation team at VCU, to study youths' perception of the risks of tobacco use and their perceptions regarding the availability of tobacco products. Here again, VTSF's consortium approach is producing advanced work across institutional lines that takes advantage both of expertise and of findings from previously disparate fields of inquiry. And as a result of the transdisciplinary thought, planning, and action fostered by VTSF funding, investigators are afforded substantial opportunity and encouragement to collaborate, thus moving Virginia to the forefront of work in tobacco-use-prevention.

## **Challenges in the offering for VYTP, and our plans for meeting them.**

### **1. To further coordinate and integrate the various, on-going VYTP and Virginia Research Consortium research projects and methodologies.**

To meet this challenge, VYTP is planning to hold quarterly meetings of our Internal Advisory Board, which consists of the principal investigators of the various currently-funded VYTP projects. These meetings provide an occasion for transdisciplinary discussion of approaches, methods, and preliminary findings, and an opportunity to anticipate and discuss possibilities for new collaborations. In particular, researchers are encouraged to identify seams or gaps in our current tobacco-research efforts, and to deploy personnel and facilities to move to close those gaps with new research and evaluation initiatives. So that these discussions proceed in a systematic and forward-looking way, we will engage a process of strategic planning that will help us refine VYTP's mission, its goals, and its objectives. This will better prepare us to anticipate research opportunities and corresponding resource needs, to shape a truly comprehensive and integrated tobacco research and evaluation program for Virginia's youth. VYTP is also in the process of soliciting nominations for an External Advisory Board to aid us in setting research priorities and garnering resources.

With respect to strengthening VYTP's role in the Virginia Research Consortium, we plan to continue faculty-to-faculty contacts to identify institutional divisions in Virginia's universities that are capable of offering or developing excellence in our field of study. In conjunction with this effort, and to help build capacity in the state for tobacco research and evaluation, consortium funding will be made available on a selective basis, through our Youth Tobacco Scholars Program, for salaries for junior faculty and post-doctoral fellows at Virginia universities. Our particular interest here is in identifying and providing mentoring relationships for scientists who are not now involved in tobacco-related work, but have knowledge and skills that can contribute to our common effort. We have also begun planning a state-wide conference on addiction and youth, where we will invite representatives from educational institutions around the state to talk about their research capabilities, plans, and accomplishments. As our experience grows in working across institutional boundaries both within and between universities, we expect to develop some large-scale, multi-institutional projects that can tackle more of the complex questions that tobacco-use poses for the Commonwealth. To facilitate these efforts, we have hired a director for the consortium, Dr. Randy Koch, who will begin work on February 25, 2003. Dr. Koch is coming to us from Virginia Department of Mental Health, Mental Retardation, and Substance Abuse, where he has held the position of Director of Research. He will also serve VCU as Executive Director of the Institute for Drug and Alcohol Studies.

**2. To further leverage VTSF funding with federal and private-foundation support for tobacco-use prevention and evaluation.**

VYTP researchers and their institutional bases already enjoy considerable grant support for their tobacco-related work. VCU's Department of Pharmacology and Toxicology is enjoying a fifteenth year of continuous funding under a National Institute for Drug Abuse (NIDA) Center Grant. This is an academic department that has published notable research on tobacco and nicotine pharmacology since the 1940s, when Paul S. Larson began his pioneering studies; and it continues that tradition of excellence and scientific leadership under Dr. Martin's direction. Currently, four VYTP-affiliated researchers in the department are recipients of NIH individual-investigator support. Also, the department is beginning its 28<sup>th</sup> year as a recipient of an NIH training grant for young investigators, making it – and Virginia – a premier attractor for the top scientists of the future. VCU's Department of Psychiatry employs a number of NIH-supported investigators at work on tobacco-related research. Dr. Kendler has been studying genes related to nicotine vulnerability with continuous funding from NIDA since 1995. Dr. Pickens has established a NIDA-funded program on women's health, which focuses in part on the special vulnerabilities of women to nicotine addiction. Dr. Patrick Sullivan is in the midst of a five-year National Cancer Institute grant studying genetic influence over the ability to quit smoking. VCU's Department of Psychology is also home to NIH-supported scholars at work on tobacco-related research, including Dr. Eissenberg, Dr. Fries, Dr. Karen Cropsey, Dr. Steven Danish, and Dr. Dace Svikis.

Because many grant projects involve the concurrent study of several substances of abuse, including tobacco or nicotine, it is not possible to put a precise dollar figure on the amount of strictly tobacco-related research in VYTP-affiliated institutions. With that caveat, and considering a snapshot of multiyear grants from all sources newly secured in 2002, based on sponsored-program data we estimate that Virginia researchers were awarded last year more than \$6 million in grant funding with direct relevance to tobacco-related research. You should note that this means that VTSF has more than doubled the new funding available for tobacco research at Virginia's universities.

This support for tobacco-related researchers and their academic departments in Virginia indicates the high level of expertise and resources that VTSF calls upon to advance its mission to understand and prevent youth tobacco use; it also indicates the scientific leverage that VTSF can command as it refines its tobacco-research objectives through the Virginia Youth Tobacco Project. VTSF funding and focus are encouraging Virginia-based researchers to devote concerted attention to tobacco and the public-health problems it engenders, especially among youth. We may expect that they will continue, and expand, Virginia's research effort in the field, and attract continuing and additional funding from the federal government and private foundations for their efforts.

### 3. To disseminate our findings so that basic research is better used to inform applied research and treatment.

The reporting of research findings is a primary objective for all VYTP researchers, and indeed for all scientists engaged in publicly funded research. In the case of tobacco research and evaluation this imperative is particularly acute, because of the urgency of the problem and the need for reliable knowledge to inform tobacco-control policy and improve tobacco-prevention programs. Below is a selected list of recent and forthcoming publications and presentations by VYTP researchers, demonstrating their commitment to disseminating the results of their work.

Breland, A.B., Acosta M.C., and Eissenberg, T. (submitted for publication) Tobacco-Specific Nitrosamines and Potential Reduced Exposure Products for Smokers: A Preliminary Evaluation of Advance™.

Breland, A.B., Buchhalter, A.R., Evans, S.E., and Eissenberg, T. (2002) Evaluating acute effects of potential reduced exposure products for smokers: clinical laboratory methodology. *Nicotine and Tobacco Research*. 4 (Suppl 2): S131-S140.

Breland, A.B., Evans, S.E., Buchhalter, A.R., and Eissenberg, T. (2002) Acute effects of Advance™: a potential reduced exposure product for smokers. *Tobacco Control*. 11:376-378.

Carroll, F.I., Lee, J.R., Navarro, H.A., Brieady, L.E., Abraham, P., Damaj, M.I., and Martin, B.R.: Nicotinic acetylcholine receptor binding, and antinociceptive properties of 2-exo-2-(2'-substituted-3'-phenyl-5'-pyridinyl)-7-azabicyclo[2.2.1]heptanes. Society for Research on Nicotine and Tobacco, Savannah, GA, 2002.

Carroll, F.I., Lee, J.R., Navarro, H.A., Ma, W., Brieady, L.E., Abraham, P., Damaj, M.I. and Martin, B.R. (2002) Synthesis, nicotinic acetylcholine receptor binding, and antinociceptive properties of 2-exo-2-(2',3'-disubstituted 5'-pyridinyl)-7-azabicyclo[2.2.1]heptanes: epibatidine analogues. *J Med Chem* 45:4755-4761.

Damaj, M.I. Activation of neuronal calcium calmoduline-kinase II after acute nicotine: behavioral and genetic approaches. Society of Neurosciences, Orlando, FL, 2002.

Damaj, M.I. Neurobiology of nicotine dependence. Society for Research on Nicotine and Tobacco, Savannah, GA, 2002.

Damaj, M.I. and Martin, B.R. Effects of nicotine and nicotinic agonists in a neuropathic pain model. World Congress on Pain, San Diego, CA, 2002

- Damaj, M.I. and Martin, B.R. Differential involvement of calcium calmoduline-kinase II in nicotine's pharmacological effects in mice. College on Problems of Drug Dependence, June, 2002.
- Damaj, M.I. and Martin, B.R. Effect of (-)-menthol on nicotine's pharmacological effects in mice. Conference on Menthol Cigarettes, Atlanta, GA, 2002.
- Donny, E.C., Lanza, S.T., Balster, R.L., Collins, L.M., Caggiula, A., and Rowell, P.P. (submitted for publication) Using growth models to relate acquisition of nicotine self-administration to break point and nicotine receptor binding.
- Dukat, M., Damaj, I.M., Young, R., Vann, R., Collins, A.C., Marks, M.J., Martin, B.R. and Glennon, R.A. (2002) Functional diversity among 5-substituted nicotine analogs; in vitro and in vivo investigations. *Eur J Pharmacol* 435:171-180.
- Dukat, M., El-Zahabi, M., Ferretti, G., Damaj, M.I., Martin, B.R., Young, R. and Glennon, R.A. (2002) (-)-6-n-Propylnicotine antagonizes the antinociceptive effects of (-)-nicotine. *Bioorg Med Chem Lett* 12:3005-3007.
- Eissenberg, T. (submitted for publication) Measuring the emergence of tobacco dependence: the contribution of negative reinforcement models.
- Eissenberg, T. (2002). Progress in nicotine and tobacco research. *Nicotine and Tobacco Research*. 4:355-362.
- Eissenberg, T., and Balster, R.L. (2000). Initial tobacco use episodes in adolescents: current knowledge, future directions. *Drug and Alcohol Dependence*. 59 (Suppl 1):S41-S60.
- Ferretti, G., Dukat, M., Giannella, M., Piergentili, A., Pignini, M., Quaglia, W., Damaj, M.I., Martin, B.R. and Glennon, R.A. (2002) Homoazanicotine: a structure-affinity study for nicotinic acetylcholine (nACh) receptor binding. *J Med Chem* 45:4724-4731.
- Fonck, C., Nashmi, R., Deshpande, P., Damaj, M. I., Marks, M. J., Schwarz, J., Collins, A. C., Labarca, C., and Lester, H.A. (in press). Increased sensitivity to agonist-induced seizures, Straub Tail, and hippocampal theta rhythm, in knock-in mice carrying hypersensitive  $\alpha_4$  nicotinic receptors. *J Neurosci*, 2003.
- Haller, D.L., Miles, D.R., and Cropsey, K.L. (submitted for publication) Smoking Stage of Change Influences Retention in Smoke-Free Residential Treatment Program for Women.
- Hamilton, D.C.P., Acosta, M., Buchhalter, A.R., and Eissenberg, T. Urine Cotinine as an Index of Smoking Status: Comparison of GC/MS with Immunoassay Test Strips. Society for Research on Nicotine and Tobacco, February 2003.
- Houtsmuller, E.J., Fant, R.V., Eissenberg, T., Henningfield, J.E., and Stitzer M.L. (2002). Flavor improvement does not increase abuse liability of nicotine chewing gum. *Pharmacology, Biochemistry, and Behavior*. 72:559-568.

- Lanni, S.M., Jansson, L., Miles, D.R., Raiford, K. and Svikis, D.S. Impact of perinatal tobacco and drug use on neonatal outcomes. Society of Maternal Fetal Medicine, New Orleans, LA, January 2002.
- Lanza, S.T., Donny, E.C., Collins, L.M. and Balster, R.L. (submitted for publication) Analyzing the acquisition of nicotine self-administration using growth curve models.
- Lee, M., Dukat, M., Liao, L., Flammia, D., Damaj, M.I., Martin, B.R. and Glennon, R.A. (2002) A comparison of the binding of three series of nicotinic ligands. *Bioorg Med Chem Lett* 12:1989-1992.
- Martin, B.R., Lukas, R.J., Eaton, B., Carroll, F.I., Navarro, H.A., and Damaj, M.I. Evidence that bupropion's pharmacological effects are primarily mediated via conversion to its 2S,3S-hydroxy metabolite. Society for Research on Nicotine and Tobacco, February, 2003.
- Maziak, W., Eissenberg, T., Klesges, R.C., Kiel, U., and Ward, K.D. (submitted for publication) Adapting Smoking Cessation Interventions for Developing Countries: A Model for the Middle East.
- Miles, D.R., Silberg, J.L., Maes, H.H., and Eaves, L.J. Testing for effects of genes, environment, and gender in tobacco initiation and continuation in adolescents: A Markov Chain Monte Carlo Approach. College on Problems of Drug Dependence, Bal Harbour, FL, June 2003.
- Miles, D.R., Silberg, J.L., Pickens, R.W., and Eaves, L.J. Gender differences in genetic and environmental risk factors for adolescent tobacco, alcohol and illicit drug use (2002). *Drug and Alcohol Dependence*, 66:S120.
- Pickens, R.W., Balster, R.L. and White, M. International Symposium on Nicotine and Tobacco Research, Santander, Spain, October 4, 2002.
- Sellers, E.M., Ibekwe, A., Martin, B.R., Glassco, W., Damaj, M.I., and Tyndale, R.F.: In vitro identification of nicotine analogs as CYP2A6 inhibitors and substrates. Society for Research on Nicotine and Tobacco. Savannah, GA, 2002.
- Wiley, J.L., Lavecchia, K.L., Martin, B.R. and Damaj, M.I. (2002) Nicotine-like discriminative stimulus effects of bupropion in rats. *Exp Clin Psychopharmacol* 10:129-135
- Zack, M., Belsito, L., Scher, R., Eissenberg, T., and Corrigan, W.A. (2001) Effects of abstinence and smoking on information processing in adolescent smokers. *Psychopharmacology*. 153:249-257.