Summary and Integration of
Virginia Foundation for Healthy Youth
Funded Research under the
Virginia Youth Tobacco Projects:
2002 through 2013

Prepared by: Alison Brelend, PhD, J. Randy Koch, PhD
& Robert Balster, PhD
Department of Psychology
Virginia Commonwealth University

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## Table of Contents

**Executive Summary** ........................................................................................................................................... 4

**Introduction and Background**

Virginia Foundation for Healthy Youth ................................................................. 8

Harm Associated with Tobacco Use ................................................................. 9

**Findings**

Research on the Basic Biology of Nicotine Addiction

Using Animal Models ....................................................................................... 11

*Comparing the effects of nicotine based on gender and age* ........................................... 11

*Neurodevelopmental effects* ........................................................................ 13

*Cognitive effects* ......................................................................................... 16

*Activity and nicotine seeking/nicotine self-administration* .......................... 17

*Other studies using animal models* ................................................................. 18

Research using Genetic Models ............................................................................. 19

*Environmental factors vs. genes* ...................................................................... 19

*Identification of specific genes and genetic mechanisms* .......................... 20

Research in the Human Laboratory ........................................................................ 22

Epidemiological Research ......................................................................................... 24

*General epidemiological studies* ..................................................................... 25

*Tobacco use and the Internet* ............................................................................ 27

*Alternative tobacco use* .................................................................................... 28

Epidemiological research with distinct populations .......................................... 29

*Smoking prevalence among adolescent girls* ................................................. 29

*Tobacco use among African-American youth* .............................................. 30

*Tobacco use among adolescents, across ethnic backgrounds* ....................... 31
Tobacco use among adolescents with behavioral health disorders ..................32
Tobacco use among sexual minority adolescents ......33

Research on Interventions for the Prevention of
Nicotine Dependence .................................................................34
Gender-specific interventions ....................................................34
Interventions for adolescents with behavioral health disorders ..................34
Other prevention programs .........................................................36

Research on Tobacco Policy and Anti-Smoking Campaigns .......39

Establishment of the Center for the Study of Tobacco Products
at VCU ..........................................................................................43

The VYTP and Student Training ....................................................44

Conclusions ..................................................................................46

Recommendations ........................................................................50

Appendices
Grants listed by Principal Investigator, 2002-2013 ...................55
References .....................................................................................64
Executive Summary

Using funds obtained from the Master Settlement Agreement, the Virginia Foundation for Healthy Youth (VFHY) supports a number of initiatives, including research on the causes, prevention, and treatment of youth tobacco use. This research has been conducted at several Virginia colleges and universities, organized under the Virginia Youth Tobacco Projects (VYTP). Using a unique multi-disciplinary research model, the VYTP has coordinated and promoted research on animal models of adolescent tobacco use, genetic studies in humans and animals, human laboratory studies, epidemiological studies, studies of prevention and treatment interventions, and policy-related studies. Prevention and treatment of tobacco use is necessary, as tobacco use results in nearly 500,000 deaths each year in the US, and it is projected that of all Virginia children currently under 18, approximately 152,000 will die prematurely from smoking. As most adult smokers (80%) began smoking before age 18, preventing smoking initiation could dramatically reduce tobacco-related deaths. However, the prevention and cessation of tobacco use is a complex issue, as tobacco use is associated with rewarding effects as well as an aversive withdrawal syndrome. In addition, psychosocial and genetic factors impact individuals’ vulnerability to tobacco use and dependence. In an effort to bolster youth tobacco prevention efforts, the VFHY has funded researchers who seek to better understand and prevent adolescent tobacco use.

Findings from work with animal models suggest that adolescents appear to be particularly vulnerable to becoming nicotine dependent. Increased sensitivity to the rewarding and negative effects of nicotine may account for adolescents’ development of dependence at lower doses of nicotine. Females may be particularly vulnerable during adolescence. In addition, concurrent use of nicotine and methylphenidate in adolescence may lead to brain and behavioral changes in adulthood, such as increased tolerance for nicotine. Findings also show that exposure to nicotine during prenatal, perinatal and adolescent periods can have lasting effects on brain development. Work with animal models has shown that nicotine can also affect learning and memory, and stress can increase the rewarding effects of even low doses of nicotine. Also, studies with animals show that exercise may prevent and treat the abuse of many drugs, including nicotine.
Findings from genetics studies indicate that there may be specific genetic factors influencing the risk for early cigarette use and for later nicotine dependence, and that environmental factors may moderate these genetic effects. Several genes likely involved in smoking initiation and nicotine dependence have been identified in animals and humans. Changes in the activation of genes have also been observed, indicating that exposure to nicotine during adolescence likely causes changes in brain development. These findings support the critical importance of preventing tobacco use in adolescents in order to avoid drug-related changes in brain development.

Human laboratory studies have also been conducted, and show that adolescent smokers self-administer nicotine and may do so to suppress withdrawal. Adolescents’ level of dependence on nicotine may also be related to psychosocial variables, such as measures of ADHD, anxiety, and family functioning. Female adolescent smokers may also have an impaired ability to identify emotions, slower reaction times, and disrupted ability to taste, possibly indicating disrupted brain functioning. Adolescents and young adult smokers may also experience deficits in cognition and perception, and may smoke in an attempt to normalize function or to improve mood. Effective interventions for adolescents should address potential psychiatric issues such as ADHD, anxiety disorders, and mood disorders, as well as cognitive issues and the adolescents’ family environments.

Results from epidemiological studies indicate that adolescents’ attitudes and beliefs about tobacco are related to their intention to smoke and to actual use of tobacco. In addition, adolescent smokers are less likely to engage in healthy behaviors in general and may use smoking as a weight management technique. Other findings show that most smokers begin smoking during adolescence, that cigarettes are often used prior to the use of other addictive substances, and that early use episodes in novice smokers usually occur in social situations involving alcohol. Further, the association between onset of regular smoking and later nicotine dependence may be particularly strong in women. Studies have also shown that girls may be more likely than boys to obtain cigarettes from friends and adults, that access to prevention programs may be limited in less affluent areas, and that youth may be obtaining incorrect information about tobacco from the internet. Prevalence data from several studies indicate that smoking rates increase from middle to high school (sometimes doubling). Also, adolescents in rural areas are more likely to smoke than those in urban areas, and in rural areas, White
adolescent females have the highest prevalence rates. Youth who are being treated for behavioral health disorders are at higher risk for tobacco use, although screening and treatment (and related training) may be limited. Studies with distinct populations provide important prevalence data, and also offer insight into particular risk and protective factors associated with different groups. Knowledge of both risk and protective factors could be used to tailor interventions for particular groups, and a more comprehensive understanding of protective factors could be applied to interventions for any population. These findings support the increased focus of VFHY prevention programs on specific segments of the population.

Intervention studies have also been conducted. Exploratory studies show that substance abuse professionals acknowledge the need for more information about gender-specific programming, and that more research-based prevention programs for adolescents with psychiatric disorders are needed. Other work has shown that researchers and community members can effectively collaborate to design a substance use prevention program. Outcomes from intervention studies have been mixed, however. Results from one intervention for youth with ADHD showed reductions in parent ratings of inattention and a reduced likelihood to try smoking. Results from another study showed that youth can learn how to become media-literate when interpreting tobacco advertisements, a potentially effective prevention technique. However, results from several other studies have shown no significant differences between intervention and control groups, suggesting that more intense interventions are probably needed.

Findings from research on tobacco control policies indicate that retailers vary in their compliance with no-sales-to-minors laws, and that successful purchases by underage buyers are related to the gender and race/ethnicity of the purchaser and the clerk. Store managers and clerks did report knowledge of the no-sales-to-minors laws, but they did not all have in-store policies to reduce sales to minors (such as requiring clerks to check IDs). Also, youth living in multi-unit dwellings may have higher exposure to second-hand smoke, and with few nonsmoking policies, may believe that smoking is normative. Other findings indicate that anti-tobacco campaigns that emphasize the negative life circumstances associated with smoking are associated with a decreased intention to smoke. Finally, research looking at education on tobacco in Virginia’s medical and dental schools shows that while the epidemiology and health consequences of tobacco use are taught, gaps exist in teaching students how to diagnose and actually treat patients.
In summary, findings from VFHY-funded studies indicate that preventing and/or treating tobacco use/dependence in adolescents is complex, and must address a variety of issues. An integrated, collaborative approach to prevention and/or treatment will likely result in the most effective methods, and VFHY-funded researchers have begun to successfully collaborate across departments and universities. For example, of the publications listed in this report, 24 involved collaborations across departments, centers, or institutes within one college/university, 22 involved collaborations across non-Virginia colleges/universities, and 8 involved collaborations across Virginia colleges/universities. In addition, all of VFHY’s currently funded research projects involve not only the funded institution but collaborating partners at other Virginia colleges/universities.

The VYTP is also one component of a much larger youth tobacco control effort in Virginia. Between FY 2007 and FY 2013, VYTP members made 100 applications to federal, state, and private organizations other than VFHY, and 49 were funded (49% of all applications submitted). In addition, VFHY funding helped lead to a much larger research grant: in 2013, VCU was awarded an $18.3 million grant by the Food and Drug Administration/National Institute on Drug Abuse to become one of 14 Tobacco Centers of Regulatory Science, nationwide. The goal of VCU’s Center for the Study of Tobacco Products is to develop and test a model for evaluating modified risk tobacco products (MRTPs) that may come to be regulated by the FDA (such as electronic cigarettes). As research shows that youth are using electronic cigarettes, and this use has been increasing (e.g., CDC, 2013), the goals of the CSTP are related to the goals of the VYTP. The VYTP is now being housed within this new innovative Center at VCU.

This report offers several recommendations for both researchers and the VFHY. For researchers, recommendations include: 1) seek collaborative research partnerships, 2) employ innovative methodologies to study novel tobacco use issues, 3) develop and design prevention intervention studies, and 4) increase external funding among VYTP/VFHY investigators. For the VFHY: 1) establish short and long-term priorities for research, 2) identify specific lines of research that are consistent with VFHY’s mission as priorities for future funding, 3) support statewide tobacco policy change and enforcement, 4) develop a system to track the impact of VFHY-funded research, 5) integrate research results into VFHY programming, and 6) continue funding support for the VYTP.
**Introduction and Background**

**Virginia Foundation for Healthy Youth**

The Virginia General Assembly established the Virginia Tobacco Settlement Foundation (VTSF) in 1999, using funds obtained from the Master Settlement Agreement with the four major US tobacco companies. Now re-named the Virginia Foundation for Healthy Youth, the VFHY funds numerous initiatives, including research on the etiology and prevention of youth tobacco use, which is the focus of this report. Research institutions participating in the Virginia Youth Tobacco Projects (VYTP) have included George Mason University, James Madison University, the University of Virginia, Virginia Commonwealth University, Virginia State University, Virginia Tech, and The College of William and Mary — these institutions make up the Virginia Youth Tobacco Projects Research Coalition. In addition, Virginia Commonwealth University serves as the coordinating center for the VYTP Research Coalition and uses a portion of its VFHY support to fund additional small grants.

In its mandate from the VFHY Board, the VYTP was charged with the responsibility to build a statewide, coordinated program of multi-disciplinary prevention research. In addressing that mandate, the Virginia Youth Tobacco Projects Research Coalition was established\(^1\). Coalition activities to date have included a small grants program, four major statewide research conferences, smaller coalition meetings (annual), and targeted funding of multi-university sponsored research projects. Since the inception of the VFHY’s research awards, investigators at the above Virginia institutions have made significant progress on issues related to youth tobacco prevention efforts, in part by collaborating across departments/centers/institutes within their own colleges/universities as well as with other colleges/universities. For example, of the 76 total publications described in this document that reported VFHY funding, 24 involved collaborations across departments, centers, or institutes within one college/university, 22 involved collaborations across non-Virginia colleges/universities, and 8 involved collaborations across Virginia colleges/universities. These numbers represent an increase over time, as shown in Table 1. In addition, many of VFHY’s currently funded research projects involve not only the funded institution but collaborating partners at other Virginia colleges/universities, as well as community partners.

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\(^1\) Principal Investigators are Dr. Bob Balster and Dr. J. Randy Koch.
Table 1. Collaborations (measured via publications)

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<td>Collaborations across departments, centers, or institutes (within a University)</td>
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This report summarizes available findings from all VFHY funded research on the causes, prevention, and treatment of youth tobacco use from 2002 through 2013. This report updates a previous report published in 2008, and another published in 2011.

Harm Associated with Tobacco Use

Tobacco use results in over 400,000 deaths each year in the US (USDHHS, 2010), and the economic costs are staggering: an estimated $ 97 billion is spent annually as a result of productivity loss and $96 billion in health-care expenditures associated with tobacco use (CDC, 2008). Importantly, most adult smokers (80%) began smoking before age 18 (CDC, 2006), and approximately 3,900 U.S. youth experiment with cigarettes for the first time each day (Garrett, Dube, Trosclair, Caraballo, Pechacek, 2011). In Virginia, approximately 21% of middle and high school students smoke (VFHY, 2012), and it is projected that of all Virginian children currently under 18, approximately 152,000 will die prematurely from smoking (CDC and USDHHS, 2006). These smoking-related illnesses and deaths are due, in large part, to the carcinogens and CO that smokers inhale. Cigarettes deliver thousands of harmful smoke constituents including carbon monoxide and carcinogens—over 60 known carcinogens are present in tobacco smoke (Hoffmann, Hoffmann & El Bayoumy, 2001). In addition, smokers also inhale nicotine, a dependence-producing drug that maintains tobacco use.
Preventing youth tobacco use could dramatically reduce these tobacco-related deaths. However, prevention of tobacco use, along with cessation of use for current users, is a complex issue. Nicotine, the active ingredient in tobacco, has a number of effects that are reinforcing for users, including euphoria, increased arousal, reduced stress, and appetite suppression (Watkins, Koob, Markou, 2000). Further, use of nicotine often leads to an aversive withdrawal syndrome during periods of tobacco abstinence (APA, 1994; Hughes & Hatsukami, 1986). Suppression of this withdrawal syndrome, via nicotine/tobacco self-administration, is thought to maintain tobacco use (USDHHS, 1988). Thus, among smokers trying to quit, relapse rates are high (Fiore et al., 2008).

In addition to the biochemical effects of nicotine, psychosocial and genetic factors impact the likelihood that individuals will become vulnerable to tobacco use and/or become dependent on tobacco. For example, lower socioeconomic status and psychiatric disorders are associated with higher incidence of tobacco use (e.g., Harwood, Slasberry, Ferketich & Wewers, 2007), and genetic factors influence tobacco initiation and dependence (e.g., Maes et al., 2004; Sullivan & Kendler, 1999). Overall, because so many factors are associated with tobacco use and dependence, developing effective prevention and cessation interventions is difficult.

Given the complex and multidimensional nature of adolescent tobacco use, the VFHY has funded a wide variety of research studies, including animal models of adolescent tobacco use, genetic studies in humans and animals, human laboratory studies, epidemiological studies, studies of interventions, and policy studies. Results are summarized below.
Findings

Research on the Basic Biology of Nicotine Addiction Using Animal Models

Preventing adolescent tobacco use begins with understanding how nicotine, the active, dependence-producing chemical in tobacco, affects adolescents’ brains. Many fundamental questions about the effects of nicotine on the adolescent brain can be addressed in laboratory settings, and one focus of funding from the VFHY has been animal studies in this area. Using animal models, questions concerning nicotine’s differential effects based on gender and age, differences in nicotine metabolism, prenatal and perinatal effects of nicotine, how nicotine impacts cognition and neuronal growth rates, as well as the potential effects of exercise on nicotine self-administration, and other questions, can all be addressed.

Comparing the effects of nicotine based on gender and age

Researchers at several of Virginia’s participating institutions received VFHY funding to explore these topics. At VCU, Dr. Billy Martin, Dr. Imad Damaj, and their team found that, in animals, nicotine affects individuals differently based on sex and age. For example, sensitivity to nicotine, reward from nicotine, withdrawal symptoms, preference, hyperalgesia (sensitivity to pain) and hyperactivity differed between male, female, adolescent, and adult mice. Male adolescent mice were more sensitive to nicotine’s effects than male adults, and the rewarding effects of nicotine were greater in male adolescents than in male adults. Preference for nicotine was also seen in male adolescents at low doses, and more hyperalgesia was seen in male adolescents than adults. In contrast, female adolescent mice were less sensitive than adults to the effects of nicotine, but experienced a worse withdrawal syndrome, as compared to adults (withdrawal measured by an increase in somatic signs, hyperalgesia and hyperactivity after nicotine cessation; Kota, Martin & Damaj, 2008). Also, adolescent males showed less hyperactivity in reaction to nicotine, compared to adult males (Kota, Martin, Robinson & Damaj, 2007).

Other studies suggest that adolescent females may be more likely to self-administer nicotine than adolescent males even when alternative rewards are available. Dr. Wendy Lynch at the University of Virginia conducted a study with rats to determine the different nicotine acquisition levels in male and female rats at the earlier and later stages of adolescence with
wheel running as an alternative to nicotine. Her findings indicate that when presented with a high dose of nicotine, both female and male rats will reliably self-administer nicotine at similar rates. However, when presented with a lower dose, females are more likely to reliably self-administer nicotine than male animals. The reason for this difference may be due to the influence of ovarian hormone levels. Specifically, ovarian hormones in female rats (such as the ratio of estradiol to progesterone) may make them more sensitive to nicotine’s effects than male rats (Lynch, 2009). In addition, Dr. Lynch and a colleague published a review paper examining the effects of the hormone progesterone on nicotine addiction. Dr. Lynch concluded that progesterone may actually reduce tobacco initiation and maintenance in females, and that progesterone may have a role in smoking cessation for women (Lynch & Sofuoglu, 2010).

Similarly, Drs. Robert Smith, Craig McDonald, Karl Fryxell and colleagues (George Mason University) have also shown that certain strains of female mice will choose to consume more of a nicotine/water solution (than water only) over time than male mice. The authors speculated that hormonal differences may explain why (Locklear, McDonald, Smith, & Fryxell, 2012).

Rate of nicotine metabolism also differs between adolescent and adult mice, which may also influence the effect of nicotine in adolescents. In humans, metabolism of nicotine involves the cytochrome P450 2A6, and mice have a corresponding homologue (CYP2A5). Dr. Joe Ritter, also at VCU, conducted some preliminary studies focusing on nicotine metabolism in mice, and found that late adolescent male mice had high CYP2A5 activity. These data suggest that nicotine metabolism and clearance may be accelerated in adolescents.

Drs. McDonald, Fryzell, & Smith have also explored the effects of concurrent nicotine and methylphenidate (Ritalin, used to treat attention deficit hyperactivity disorder) exposure in adolescent rats, and the effects as those rats became adult animals. They found that those animals who were exposed to both nicotine and methylphenidate as adolescents showed more tolerance to nicotine as adults (as measured by activity in response to nicotine; animals who received both nicotine and methylphenidate as adolescents were less active in response to nicotine as adults). Exposure to both drugs in adolescence also led to changes in mRNA (molecules involved in carrying genetic information). These findings suggest that concurrent use of nicotine and methylphenidate in adolescence leads to brain and behavioral changes in adulthood (Wheeler, Smith, Bachus, McDonald, Fryxell, & Smith, 2013).
Overall, findings in this area suggest that adolescents appear to be particularly vulnerable to becoming nicotine dependent. Increased sensitivity to the rewarding and negative effects of nicotine may account for adolescents’ development of dependence at lower doses of nicotine. Females may be particularly vulnerable during adolescence, and accelerated nicotine metabolism in adolescents may also affect the development of dependence. In addition, concurrent use of nicotine and methylphenidate in adolescence may lead to brain and behavioral changes in adulthood, such as increased tolerance for nicotine. Understanding the differences in vulnerability among these different groups will be valuable in forming targeted strategies for prevention and treatment.

**Neurodevelopmental effects**

Numerous studies have been conducted examining potential neurodevelopmental effects of nicotine. For example, Dr. Susan Robinson from Virginia Commonwealth University has demonstrated that nicotinic acetylcholine receptors, or nAChRs, are more active during adolescence than during adulthood. Moreover, her findings demonstrate that consumption of nicotine in the earlier stages of adolescence, when the brain is still developing, increases activity of nAChRs. In other words, nicotine exposure in early adulthood is likely to result in significant biological changes that may lead to an increased likelihood of nicotine addiction in adulthood (Kota, Robinson & Damaj, 2009).

Dr. Robinson and colleagues have also explored both prenatal and perinatal exposure (that is, exposure in the time surrounding birth) to nicotine; both may influence the effect of nicotine on adolescents. First, Dr. Robinson and colleagues conducted a study to determine the effects of perinatal exposure on later receptor response. Pregnant rats were administered nicotine on gestational day 7, and after birth and some maturation, the rat pups’ brains were exposed to nicotine, and nicotinic acetylcholine receptor response was measured. Results indicated that the normal peak in nicotinic acetylcholine receptor response was eliminated by perinatal nicotine exposure. There are several potential implications of this finding—first, if perinatal exposure to nicotine reduces an adolescent’s response to nicotine, this might cause an adolescent to smoke more frequently to achieve the rewarding properties of nicotine. Second, adolescents perinatally exposed to nicotine might experience cognitive deficits and smoking could help them to compensate. Third, other types of nicotinic acetylcholine receptors (not studied here) may
actually be increased by perinatal nicotine exposure, thus making an adolescent more sensitive to the effects of nicotine (Britton, Vann & Robinson, 2007).

In another study, Dr. Robinson and colleagues also found that when adolescent rats are exposed to nicotine in their prenatal period, they become less sensitive to nicotine than their non-exposed peers and had levels of nicotine sensitivity similar to adult animals. This finding may contradict the popular belief that children are more likely to become smokers if exposed to nicotine prenatally via the mother’s smoking. Alternatively, as noted above, this finding may indicate that children exposed to nicotine in utero may need to use more nicotine to achieve the rewarding effects of nicotine. In her further studies, Dr. Robinson and colleagues want to conduct additional research on this issue and to identify nicotine receptors that are directly responsible for nicotine addiction.

At George Mason University, Dr. Robert Smith and colleagues have also studied the effects of nicotine exposure during the prenatal and early postnatal periods. His findings reveal that exposure to nicotine during those periods leads to changes in brain development that carry on into adolescence. Implications of his work suggest that using nicotine replacement therapy (such as the nicotine gum or nicotine patch) during pregnancy may also affect fetal brain development (Eppolito, Bacchus, McDonald, Meador-Woodruff & Smith, 2010).

Additional work in animals has shown that during adolescence, nicotine exposure causes powerful, lasting effects on the brain. Dr. Robert Smith and his colleagues have focused on the nature of these long-lasting effects. For example, nicotine exposure in adolescence can lead to changes in many different aspects of brain development, which then affects nicotine addiction, reward and emotions. Indeed, Dr. Smith’s work has shown that early nicotine exposure—even just one injection in an adolescent animal—can make that animal more sensitive to the effects of nicotine as an adult (Brielmaier, McDonald & Smith, 2007). Additionally, adolescent nicotine exposure can result in stronger negative emotions (i.e., more of a fear response as adults; Smith et al., 2006), and can cause deficits in spatial learning (Eppolito & Smith, 2006). Dr. Smith and colleagues have also been able to specify the regions in the brain and types of neurons on which nicotine exerts its’ effects on development (Bergstrom, McDonald, French & Smith, 2008; McDonald et al., 2007; McDonald et al., 2005). These important neural findings suggest that initial exposure to nicotine as an adolescent may cause significant changes in the brain that persist throughout adulthood, and which contribute to the cycle of tobacco dependence.
Dr. Smith and colleagues have also studied the specific periods during which adolescents are most susceptible to nicotine’s effects, and have found that exposure in early adolescence produces more changes than exposure later in adolescence. They have also studied how short-term nicotine dosing affects fear responses, and found that these effects are seen even after just six injections with nicotine. Additionally, this team observed maximal sensitization to nicotine in adolescents after just 3 injections (in contrast to 8 in adults).

In addition to nicotine consumption in adolescence, Dr. Smith’s research also indicates that factors like stress and the presence of others during nicotine exposure affect future reactions to nicotine. Smith’s work suggests that brain systems that are responsible for stress mediation closely interact with systems that mediate nicotine’s effects. For example, animals that experienced stress later showed a preference for lower doses of nicotine compared to animals that did not experience stress. In another study of stress, the presence of another animal during adolescent consumption of nicotine decreased the effects of nicotine during later nicotine challenges. Other studies conducted by Dr. Smith and his colleagues have examined the effects of adolescent nicotine exposure anxiety as adults, the effects of bullying as well as prosocial behavior on nicotine consumption in adolescence, and the differences in reactions to nicotine in adolescents and adult animals’ brains.

In 2012, Drs. Smith and McDonald from George Mason University received a VFHY grant to continue their work studying adolescent vulnerability to the neurodevelopmental effects of nicotine. As of July, 2013, they reported that nicotine-induced growth of dendrites (part of a neuron), but not dendritic spines (a specific part of the dendrite) was inhibited by blocking D1 dopamine receptors. This finding indicates that D1 dopamine receptors are part of the mechanism by which nicotine is increasing dendritic growth, but that other mechanisms are involved in the growth of dendritic spines. Drs. Smith and McDonald are also investigating the MAPK second messenger system (molecules that send messages inside cells), which may also be involved in this mechanism. These findings that nicotine is changing the adolescent brain increase the importance of prevention efforts.

Dr. Karl Fryxell at George Mason University also received a VFHY grant in 2012, which is focusing on adolescent nicotine use and the effects of stress and social isolation. Work is currently underway. Dr. Fryxell and colleagues will also be looking at the effects of nicotine on
protein and mRNA levels in mice to better understand the specific gene responses to nicotine, in adolescent animals.

Overall, findings from Dr. Robinson’s and Dr. Smith’s research indicate that exposure to nicotine during prenatal, perinatal and adolescent periods can having lasting effects on brain development, and are a significant contribution to research on the neurodevelopmental impact of nicotine. Research from Dr. Fryxell’s work will provide important additional information on the effects of stress and social isolation on adolescent nicotine use.

Cognitive effects

Nicotine can also affect learning and memory. At the College of William and Mary, Drs. Robert Barnet, Joshua Burk, and Pamela Hunt were funded to conduct research on the effects of adolescent nicotine exposure on learning and memory, using an animal model. The learning involved in fearful situations (such as an animal learning to freeze in response to a light paired with a shock to the feet, and variations on this paradigm) is often used to better understand brain mechanisms involved in learning and memory. Dr. Barnet and colleagues found that in some paradigms, injections of nicotine during adolescence enhanced learning of fear. However, when nicotine-exposed adolescents were again exposed to nicotine as adults, learning was impaired. Additional work has also shown that another type of learning (context conditioning) is impaired when adolescent animals are chronically exposed to nicotine (Spaeth, Burk, Barnet & Hunt, 2010). Further research by this group indicates that nicotine causes long-term changes in the hippocampus, a region of the brain important for learning and memory.

Dr. Barnet and colleagues have also investigated differences in the duration of nicotine exposure on learning, and additional brain areas that may be involved. For example, Dr. Burk has studied how larger doses of nicotine (“binges”) affect learning and memory in animals. Results revealed that when animals receive large, chronic doses of nicotine, learning is impaired in some paradigms, which indicates damage to the hippocampus. These findings show that nicotine exposure can affect brain systems involved in learning and memory, and begin to explain the specific nature of the impairments.

Dr. Damaj and colleagues at Virginia Commonwealth University have explored the effects of learning and memory on nicotine reward, in adult and adolescent mice. Both adult and adolescent mice learned that they would receive nicotine injections on only one side of a box (the
paradigm is called “conditioned place preference”), and saline injections on either side of the box. Mice are then tested, to see what side they prefer (even when given no injection). After several days of receiving injections, both adult and adolescent mice preferred the drug-paired side of the box. However, after the injections had stopped (“extinction”) adolescent mice continued to prefer the drug-paired side of the box for more days than adult mice. Also, when the nicotine injections were started again, adolescent mice showed a preference again for the drug-paired side of the box, where adult mice did not. These results suggest that adolescent mice may be more sensitive to the rewarding effects of nicotine, and that memory may be involved (Kota, Sanjakdar, Marks, Khabour, Alzoubi, & Damaj, 2011).

Drs. Brielmaier, McDonald, and Smith (George Mason University) have also studied the effects of stress on conditioned place preference in adolescent, male rats. Animals were exposed to a footshock (a stressful event for a rat) or no footshock before receiving injections of nicotine and being placed on a certain side of a box. Rats who received the footshock prior to the injections were more likely to stay on the “nicotine” side of the box when receiving low and high nicotine doses. Rats who received no footshock prior to injections only stayed on the “nicotine” side of the box when receiving a high nicotine dose. This suggests that stress can increase the rewarding effects of even low doses of nicotine among adolescent rats. In a second experiment, Drs. Brielmaier and colleagues also gave the rats a drug to reduce stress (a corticotropin-releasing factor type 1 receptor antagonist); rats who received the medication before the footshock were not more likely to stay on the “nicotine” side of the box after low doses of nicotine. This suggests that the medication reduced stress, and that the corticotropin-releasing factor type 1 receptor is involved in stress increasing the rewarding effects of nicotine (Brielmaier, McDonald, & Smith, 2012).

Activity and nicotine seeking/nicotine self-administration

Several VFHY-funded investigators have examined the relationship between activity and nicotine consumption. For example, Dr. Smith from GMU has conducted research showing that nicotine consumption increases activity in adolescent rats but decreases activity in adult rats. Dr. Smith plans to conduct future research further examining this relationship, including how anxiety may be involved.
In addition, Dr. Darlene Brunzell from Virginia Commonwealth University, and Dr. Wendy Lynch from UVA used an animal model to determine if exercise during a cessation period can effectively reduce relapse to adolescent nicotine seeking. Rats were trained to self-administer nicotine for a period of time, and then the nicotine was taken away for another period of time (similar to a quit attempt in humans). Once the nicotine was taken away, some animals were allowed access to a running wheel, while others were not. Afterwards, access to the lever that previously gave nicotine became available again to all animals. Findings indicated that animals allowed to exercise showed significant reductions in nicotine seeking behavior following exercise. These findings suggest that there is a biological link between activity and nicotine self-administration, and may be applicable to prevention and cessation interventions in humans (Sanchez, Moore, Brunzell, & Lynch, 2013a). Drs. Brunzell, Lynch, and colleagues also examined sex differences in the relationship between nicotine seeking behavior and exercise. They found that access to exercise (a running wheel) reduced nicotine-seeking behavior in male rats. In female rats, access to either a locked or unlocked running wheel reduced nicotine-seeking behavior (Sanchez, Moore, Brunzell, & Lynch, 2013b). This indicates that, in girls, exposure to novelty and environmental enrichment may also work for smoking relapse prevention. Finally, Dr. Lynch and colleagues also published two review articles describing how studies with animals show that exercise may be a potential treatment for the abuse of many drugs, including nicotine (Smith & Lynch, 2012), and the parameters under which exercise may be the most beneficial (Lynch, Peterson, Sanchez, Abel, & Smith, 2013).

Drs. Brunzell and Lynch were again funded for the 2012-2015 period, and are currently working to understand sex differences in the prevention of nicotine self-administration among adolescent animals. Preliminary results suggest that for female rats, exercise or environmental enrichment can disrupt nicotine self-administration. For male rats, only exercise seems to disrupt nicotine self-administration. Drs. Brunzell and Lynch are also looking at specific brain areas in male adolescent rats to determine the effects of nicotine, and of exercise.

Other studies using animal models

Dr. Brunzell (VCU) has also used an animal model to better understand the relationship between tobacco use and schizophrenia, as most individuals with schizophrenia are smokers. Dr. Brunzell and her team hypothesized that schizophrenics may have fewer alpha 7 nicotinic
acetylcholine receptors in certain areas of their brains. In an animal model, Dr. Brunzell’s team blocked this type of receptor (with medication) in rats, and found that this blocking increased rats’ nicotine seeking behavior and nicotine intake. Another medication (a nicotine agonist, which affects receptors similarly to nicotine) was also administered, and reduced nicotine intake. Dr. Brunzell and colleagues concluded that reduced nicotinic acetylcholine receptors could be a reason for increased tobacco use among schizophrenics (Brunzell & McIntosh, 2013).

Finally, in new work, Dr. Nadine Kabbani from George Mason University recently received a VYTP small grant to study the effects of menthol flavoring on cigarette addiction, from a molecular perspective. No results are yet available.

Research using Genetic Models

*Environmental factors vs. genes*

Studying how genetics influence the initiation of and dependence on nicotine/tobacco is another focus of VFHY-funded studies. Dr. Billy Martin, Dr. Kenneth Kendler, and colleagues at VCU have conducted studies of genetics in both human and animal models. In humans, twin studies are often used to distinguish between the effects of genetics and the environment, and using data from the Virginia Twin Registry, Dr. Kendler’s team has demonstrated that genetic factors play a significant role in how likely an individual is to initiate smoking (Maes et al., 2004). Further, genetic factors influencing the risk for nicotine dependence appear to be substance-specific (one genetic factor does not explain dependence on all common drugs of abuse; Kendler, Myers, & Prescott, 2007). Dr. Roy Pickens and Dr. Donna Miles at VCU have also analyzed data from twin studies, which indicate that several environmental factors (such as family adaptability, cohesion, parental discipline and leadership) may moderate the genetic influence for risk of tobacco use among adolescent females. Other results indicate that additive genetic, shared environmental, and unique environmental factors significantly influence tobacco use, and that additive genetic and unique environment factors significantly impact the heritability of becoming a daily smoker (for a review, see Maes & Neale, 2009). Dr. Kendler’s group is continuing work in this area, and has found that social environmental factors influence early cigarette use, while genetic factors become more important in later cigarette use. More recently, Drs. Kendler, Damaj, Chen, and colleagues reported that among identical twins (with the same genetic material) who were both smokers, the twin who began smoking earlier had increased
nicotine dependence. This suggests that earlier exposure to nicotine affects the level of later dependence (Kendler, Myers, Damaj, & Chen, 2013).

Overall, these findings suggest that prevention programs should incorporate the family and include a component that educates parents on how their interactions may influence their children’s substance use behavior. Also, this work shows that prevention programs which completely prevent or even delay smoking initiation are important for preventing later smoking dependence.

Identification of specific genes and genetic mechanisms

Further work has been conducted to examine which genes are involved in tobacco initiation and dependence, beginning with animal studies. For example, animal models have been used to determine differences in gene expression (how genes affect cells) in particular brain regions after nicotine administration. These results can then be applied to humans by studying differences in the specific genetic makeup of smokers vs. non-smokers, as well as differences between smokers with different levels of dependence. Results from Dr. Kendler’s work in this area suggest that the PTEN gene and the OPRM1 gene may be involved in both smoking initiation and nicotine dependence (Zhang, Kendler & Chen, 2006a; Zhang, Kendler, & Chen, 2006b). In addition, Dr. Michael Miles identified a gene in mice (RhoA) related to nicotine response, and also found that the related human gene is associated with smoking initiation and nicotine dependence (Chen et al., 2007). Dr. Xiangning Chen and colleagues have also conducted research suggesting that the cannabinoid receptor 1 (CRN1) gene may be implicated in nicotine dependence, and that the association of this gene with nicotine dependence may be sex-specific (Chen et al., 2008). Dr. Chen and colleagues have also shown that single nucleotide polymorphisms of the genes CHRNA5 and CHRNA3 were associated with nicotine dependence (Chen et al., 2009). Dr. Chen and colleagues (including Drs. Brunzell, Damaj, and Kendler) have also conducted a series of studies and a meta-analysis to show that the ACSL6 gene may be associated with how many cigarettes individuals smoke (Chen et al., 2011). Finally, Dr. Brunzell recently published a review article focused on how the activation of αβ2 subunit nicotinic acetylcholine receptors is involved in nicotine use. Medications (such as varenicline) that inhibit these receptors can help with tobacco cessation (Brunzell et al., 2012), although use of these medications in adolescents is rare.
Significant work has also been conducted by other researchers at Virginia Commonwealth University. Dr. Imad Damaj, along with other investigators, used an animal model to better understand the genetic mechanisms involved in nicotine dependence. In their study, mice with two different phenotypes (D2 and B6) were compared in their response to chronic nicotine use. Findings include that one group of mice (with the D2 phenotype) were not as sensitive to the effects of nicotine, and had fewer withdrawal signs when nicotine was discontinued. These findings suggest that these particular strains of mice may be helpful in future studies which seek to identify genes involved in nicotine use and dependence (Jackson, Walters, Miles, Martin, Damaj, 2009).

At GMU, Dr. Smith, Dr. Karl Fryxell, and colleagues have also studied the effects of nicotine exposure on gene expression in adolescent animals. Nicotine exposure during adolescence induces changes in gene expression, leading to changes in many different aspects of brain development. Further, changes in gene expression after chronic nicotine administration had the greatest effects on female rats near the age of puberty, which may partly explain how human smoking initiation develops during adolescence. Drs. Smith and Fryxell also found that gene regulation was more intense in the hippocampus than other brain regions, and that several of the genes investigated are involved in the regulation of dopamine neurons (dopamine is often related to reward-seeking behavior) (Polesskaya, Fryxell, et al., 2007). Additional research has shown that for female animals, chronic exposure to nicotine in adolescence decreased expression of gene Pde4b in certain brain areas associated with drug addiction and learning. Interestingly, the expression of Pde4b is also inhibited by some anti-depressants, suggesting a mechanism for the link between depression and smoking (Polesskaya, Smith, & Fryxell, 2007). More recently, Dr. Fryxell has been using an animal model of adolescent’s first use of nicotine and how that reaction predicts later vulnerability to nicotine addiction. In human adolescents, the response to the first cigarette (for example, feeling dizzy or relaxed) can predict later nicotine dependence. Using different strains of adolescent mice, Dr. Fryxell’s team has observed that an animal’s first reaction to nicotine in adolescence does predict vulnerability to nicotine addiction in adulthood. Further, different strains of mice had different gene expression responses and differences were also observed across genders.

Drs. Smith and McDonald (GMU) and colleagues also looked at animals of different ages (early adolescents, late adolescents, and adults), to determine the relationship between anxiety-
like activity (after injections of nicotine) and dopamine receptor mRNA expression. They found differences between the adolescent and adult animals, in terms of the relationship between activity and dopamine receptor expression. These results provide further support for the idea that the addictive potential of nicotine changes across the lifespan (Falco, McDonald, Bachus, & Smith, 2014).

Recently, Dr. Michael Scott (UVA) received a VYTP small grant to study the epigenetic effects (changes in gene activity not related to changes in DNA sequence) of nicotine in adolescent and adult rodents. Dr. Scott will specifically examine how nicotine affects demethylation (the removal of a methyl group from a DNA nucleotides, related to gene expression) in nuclei of the brain.

Taken as a whole, these studies indicate that there may be specific genetic factors influencing the risk for early cigarette use and for later nicotine dependence, and that environmental factors may moderate these genetic effects. Several genes likely involved in smoking initiation and nicotine dependence have been identified in animals and humans. Importantly, changes in gene expression have been observed in animal models of adolescent nicotine exposure, indicating that exposure to nicotine during adolescence likely causes changes in brain development. These findings support the critical importance of preventing tobacco use in adolescents in order to avoid drug-related changes in brain development. Prevention and treatment interventions also need to address adolescents’ environments.

**Research in the Human Laboratory**

Studying adolescents in a human laboratory setting can also provide key information about youth smoking, such as the effects of smoking on various biomarkers, and the relationship between biomarkers, withdrawal symptoms, and other variables. Several VFHY-funded studies have been conducted using human laboratory methodology. For example, a number of current and former VCU researchers (Drs. Tom Eissenberg, Deborah Haller, Karen Ingersoll, Carolyn Heckman and Alison Brelan) were involved in a study focused on the smoking behavior and psychosocial characteristics of adolescent smokers with low nicotine dependence (participants smoked an average of 3.64 cigarettes per day and had low dependence scores). Results showed that even these adolescents experienced significant increases in saliva nicotine and heart rate, and reported that smoking reduced their withdrawal symptoms. These investigators also found
significant associations between psychosocial variables (such as a measure of conduct disorder), and nicotine dependence scores, as well as significant associations between psychosocial variables (such as measures of ADHD, anxiety, and family functioning) and withdrawal measures.

Researchers at Virginia Tech have also conducted several studies in laboratory settings with human participants. In one study, Dr. Helen Crawford and Dr. Li Wan assessed adolescent female smokers and nonsmokers for differences in emotion recognition, cognition, and several dependence and psychosocial measures. Results showed that smokers had more difficulty correctly identifying emotions and had more cognitive control difficulties than non-smokers, and that smokers with higher nicotine dependence scores had slower reaction times and disrupted ability to taste. The authors conclude that these findings provide support for the orbitofrontal/disinhibition model, which postulates that addiction disrupts the function of the orbitofrontal cortex, a brain region involved in facial expression recognition, emotions, and olfaction (Crawford, Loe, & Wan, 2004).

Additional research indicated that among adolescent and young adult smokers, daily smoking was associated with more deficits in cognition, perception, and names lapses (Wan, Friedman, Boutros, & Crawford, 2008). In another study, the relationship between smoking, schizotypal personality and cognition were assessed. Smokers with high scores on a measure of schizotypal personality performed better on a test of sensory gating (the ability to ignore irrelevant sensory input) than smokers with lower scores. In contrast, non-smokers with high scores on a measure of schizotypal personality scored worse on a test of sensory gating than non-smokers with low scores. This finding suggests that tobacco may help normalize the ability to ignore irrelevant sensory input in some individuals (Wan, Crawford, & Boutros, 2006).

In another study, Dr. Craig McDonald from George Mason University sought to identify the relationships between executive functioning (that is, the management and control of cognitive processes) and nicotine exposure in adolescence; the primary aim was to examine if executive functioning is compromised in young adult tobacco users. Dr. McDonald studied 15 smokers and 15 nonsmokers, who completed a cognitive task requiring inhibitory control (go/no-go task) while the electroencephalogram (EEG) was recorded. He found that an electrophysiological index of inhibitory control was reduced in smokers (although no differences
were observed between groups on the go/no-go task). This finding may indicate that nicotine is changing brain function, or, that smokers have a pre-existing impairment in cognitive control, rendering them vulnerable to tobacco use (Buzzell, Fedota, Roberts, & McDonald, 2014).

Another laboratory study was conducted to explore the relationship between smoking and activity of the human platelet monoamine oxidase-B (MAO-B) in smoking and non-smoking adolescent females. MAO-B is significantly lower in adult smokers than non-smokers, and tobacco may inhibit MAO-B, thus changing neurotransmitter levels and possibly having an antidepressant effect (for review, see Lewis, Miller, Lee, 2007). Results from this laboratory study also showed that smokers had significantly lower MAO-B levels than non-smokers (Castagnoli, Wu, & Crawford, 2004).

Recently funded by a VYTP small grant, Dr. Warren Bickel and Dr. Jungmeen Kim-Spoon at Virginia Tech will be using a human laboratory study to assess self-control failure in adolescent smokers. Specifically, they will assess the extent to which adolescent smokers discount future rewards, and the relationship between that discounting and environmental variables such as stress. Results are not yet available.

Overall, findings from human laboratory studies show that adolescent smokers self-administer nicotine and may do so to suppress withdrawal. Adolescents’ level of dependence on nicotine may also be related to psychosocial variables, such as measures of ADHD, anxiety, and family functioning. Female adolescent smokers may also have an impaired ability to identify emotions, slower reaction times, and disrupted ability to taste, possibly indicating disrupted brain functioning. Adolescents and young adult smokers may also experience deficits in cognition and perception, and may smoke in an attempt to normalize function or to improve mood. Effective interventions for adolescents should address potential psychiatric issues such as ADHD, anxiety disorders, and mood disorders, as well as cognitive issues and the adolescents’ family environments.

**Epidemiological Research**

A major focus of VFHY funding has been epidemiological research in a variety of areas. The goals of these studies include obtaining a better understanding of tobacco use prevalence rates, risk and protective factors, related health behaviors, beliefs, attitudes about smoking,
where tobacco is obtained, access to prevention programs, and how the internet can play a role in tobacco use.

**General epidemiological studies**

At VCU, Dr. Elizabeth Fries and colleagues conducted research on several psychosocial factors associated with adolescents’ intention to smoke. These researchers surveyed high school students from rural Virginia, using questions about attitudes toward tobacco, smoking prevalence, and intentions to try smoking. Results indicated that among non-smokers, a decreased likelihood of intention to smoke was associated with having favorable attitudes toward being tobacco free, having fewer friends who smoke, and perceiving quitting smoking to be difficult (Smith, Bean, Mitchell, Speizer, & Fries, 2007). Additional research on middle and high school students showed that adolescent smokers were less likely to engage in healthy behaviors, such as consuming vegetables and milk/dairy products, and exercising, compared to adolescent non-smokers (Wilson et al., 2005). In another study, these researchers examined attitudes toward smoking and weight loss among nonsmokers, experimental smokers, and current smokers in high school. In this study, current smokers were more likely to believe they would gain weight if they quit smoking, compared to nonsmokers and experimental smokers (Bean et al., 2008). Further support for the relationship between smoking and weight was reported by Drs. Heckman and Ingersoll at VCU, who found that among a small group of adolescent experimental smokers, smoking was sometimes used for weight management. Also, these experimental smokers who smoked for weight management were more likely to be users of alcohol, and more likely to experience alcohol-related problems. All of these studies highlight the relationship between smoking, beliefs about smoking, and health behaviors, and provide support for the need to address these issues in tobacco prevention and cessation programs.

Longitudinal epidemiological research has also been conducted by VFHY-funded researchers. Dr. Bruce Dembling at the University of Virginia, along with Dr. Carol Prescott at VCU, jointly studied how early exposure to nicotine affected the later probability and severity of substance abuse/dependence. Dr. Dembling analyzed data from the National Household Survey on Drug Abuse (NHSDA) for 1994-2002 (325,710 subjects 13 years of age and older). Results indicated that cigarettes were used prior to other addictive substances, and that most smokers (90%) began smoking by age 18. In addition, early cigarette use was strongly associated with later development of nicotine dependence and use of other drugs.
Dr. Prescott analyzed similar variables from the Virginia Adult Twin Study of Psychiatric and Substance Use Disorders (VATSPSUD), and found similar results. Specifically, earlier onset of regular smoking was associated with later risk for nicotine dependence and use of other drugs, and this association was more marked in women. Also, risk for using other drugs was related to co-twin onset of regular smoking. Combined, the results of Drs. Dembling and Prescott show that most tobacco use begins during adolescence, and that earlier use is associated with risk for dependence and use of other substances.

In addition to traditional survey techniques, several VFHY-funded researchers have conducted focus groups to gain a more comprehensive understanding of attitudes and beliefs about smokers and smoking. At UVA, Dr. Pamela Kulbok explored nonsmoking attitudes, beliefs, and strategies in 16-17 year old non-smokers and former experimenters. Results showed that participants opposed stereotyping of non-smokers; viewed nonsmoking as a personal choice; identified issues of “self-control,” “having a reason not to,” and “having friends who support them.” These non-smokers also reported concerns about health, addiction, cost and being “too cute to smoke.” Nonsmoking was also reinforced by the approval of parents, friends, and by personal beliefs. Results also showed that youths who experimented with smoking were more open to interacting with teenage smokers than youths who never tried smoking. Dr. Kulbok concluded that multiple approaches to prevention targeting adolescents’ attitudes, family and peer networks are warranted.

At James Madison University (JMU), Dr. Monica Reis-Bergan also conducted focus groups with a range of students (middle school, high school and 1st year college students), and asked what factors influenced their decision to smoke or not smoke. Some of the participants’ beliefs about choosing to smoke included statements of fitting in, having something to do, coping with stress, and feeling good. Among females only, statements included smoking to have one’s boyfriend like them, and to stay thin or lose weight. Also, among 1st year college students, smokers were more likely than non-smokers to report feeling fat, binging on food, using laxatives or diuretics, and fasting or skipping two meals in a row. Among smoking and non-smoking 1st year college students, 11% met the criteria for an eating disorder, and of those, 30% smoked a few times a month or more, and 18% smoked everyday.

VFHY funding also contributed to the analysis of data collected in a large study of smoking initiation among older adolescents (Acosta et al., 2008). Students reported early
tobacco use episodes using weekly internet-based data collection methods and when smoking initiation was detected, detailed questions about the circumstances were asked. It was found that 90% of smoking occurred in social settings, many where alcohol was also used. Students reported that they smoked in part because it was the norm at drinking parties and everyone did it. The authors concluded that reducing alcohol consumption in youth would have the added benefit of reducing tobacco use and that youth prevention approaches that address the alcohol-smoking connection seem warranted by these data (Acosta et al., 2008).

Finally, VFHY-sponsored research at Virginia Tech by Dr. Christine Kaestle has focused on analysis of the Virginia Youth Tobacco Survey. In one study, Dr. Kaestle examined differences between boys and girls in terms of how tobacco is obtained. Results showed that girls were more likely to obtain free cigarettes, cigars, and cigarillos (for example, from adults and friends) than boys. In contrast, when obtaining smokeless tobacco, girls were more likely than boys to purchase these products (Kaestle, 2009). In another study, Dr. Kaestle examined factors at the individual and neighborhood levels that lead to smoking and whether or not tobacco prevention programs target neighborhoods with the most need. Dr. Kaestle looked at two data sources to answer her questions: the 2005 Virginia Youth Tobacco Survey and The Census 2000 School District Demographic Project. Her findings demonstrated that low, medium and high rates of cigarette use were associated with low economic status and that students attending schools in lower socio-economic communities had less access to prevention programs than the areas with greater wealth and lower rates of smoking. These findings suggest that efforts should be made to implement school-based prevention programs in communities with the greatest need (Kaestle and Wiles, 2010).

Tobacco use and the Internet

A recent study examined the content of internet messages and effects of social media on tobacco use. Researchers at Virginia Commonwealth University, Dr. Aashir Nasim and Dr. May Kennedy, conducted a study to identify specific characteristics of YouTube videos that promote tobacco use. Drs. Nasim and May, along with colleagues, conducted both a content analysis study and a thematic analysis study of the videos that involved cigar smoking. Specifically, they examined videos that showed “freaking”—removing the binder from a cigar before smoking it. Findings showed that there was a multi-step technique to removing the paper, and that users
believed that removing the paper would make the cigar healthier and easier to smoke (Nasim, Blank, Cobb, Berry, Kennedy, & Eissenberg, 2014). Some initial findings from this study were also used in another related research project on cigarillos in collaboration with other VCU researchers (Blank, Nasim, Hart & Eissenberg, 2011).

Results from these epidemiological studies indicate that adolescents’ attitudes and beliefs about tobacco are related to their intention to smoke and to actual use of tobacco. In addition, adolescent smokers are less likely to engage in healthy behaviors and may use smoking as a weight management technique. Other findings show that most smokers begin smoking during adolescence, that cigarettes are often used prior to the use of other addictive substances, and that early use episodes in novice smokers usually occur in social situations involving alcohol. Further, the association between onset of regular smoking and later nicotine dependence may be particularly strong in women. More recent studies have shown that girls may be more likely than boys to obtain cigarettes from friends and adults, that access to prevention programs may be limited in less affluent areas, and that youth may be obtaining incorrect information about tobacco from the internet.

**Alternative tobacco use**

Dr. Nasim and colleagues at VCU have also conducted several epidemiological studies of alternative tobacco use (for example: cigars, cigarillos, smokeless tobacco, bidis/clove cigarettes, and waterpipe tobacco smoking) among youth. In one study, Dr. Nasim and colleagues conducted a secondary analysis of data from the National Youth Tobacco Survey, and found that from 1999-2009, light cigarette smoking and smokeless tobacco use increased. Heavy cigarette smoking and bidi/clove use decreased (Nasim, Khader, Blank, Cobb, & Eissenberg, 2012).

Additional work using the Virginia Youth Tobacco Survey (2009 data) showed that alternative tobacco use was linked to use of cigarettes, as well as age of initiation of cigarette use. Early onset of cigarette smoking was a stronger predictor of use of alternative tobacco products among African American youth, as compared to white youth (Nasim, Blank, Cobb, & Eissenberg, 2013). Finally, Dr. Nasim and colleagues conducted additional analysis of the Virginia Youth Tobacco Survey (2009 data), looking specifically at cigar use among youth. They reported that over half of youth who said they used Black & Milds (a type of cigar), did not
say they used cigars generally. This finding indicates that surveys with general questions about cigar use may underestimate actual use (Nasim, Blank, Berry, & Eissenberg, 2012).

*Epidemiological research with distinct populations*

Some VFHY-funded studies have specifically examined prevalence rates and risk and preventive factors among distinct populations such as adolescent girls, adolescents from a variety of ethnic backgrounds (including African-Americans), adolescents with behavioral health disorders, and sexual minorities.

*Smoking prevalence among adolescent girls*

At Virginia Tech, Dr. Peggy Meszaros and colleagues examined smoking prevalence among adolescent girls, using data from four nationally representative surveys (dates ranged from 1991 to 2002). Wide ranges in prevalence rates were observed. For example, for lifetime cigarette use, rates ranged from 31% to 72%; for current smoking, from 22% to 28%; and for smoking in the last month, from 9% to 39%. The authors suggested that differences in methodology and analysis account for these differences. Other results showed that current smoking prevalence rates among middle school girls (approximately 10%) are about half that of high school girls. Also, White female adolescents had the highest rates of smoking, with Hispanic, Black, and Asian girls reporting less (Matheson, Meszaros, Huebner, Piercy, & Davis, 2004).

Dr. Meszaros and colleagues have also focused their research on risk factors for tobacco use among adolescent girls. A review of the research indicates that many factors (i.e., individual, parental, and peer-related) are associated with smoking behavior in female adolescents (Huebner et al., 2004). Dr. Meszaros and colleagues also examined a number of these factors among female smokers living in rural Virginia who reported being current or former smokers. Results showed that, in contrast to current smokers, former smokers reported lower levels of delinquency, less coping by taking drugs, less alcohol and marijuana use, and less cigarette availability. Former smokers also reported less depression, fewer suicidal thoughts, and fewer suicide attempts. Finally, former smokers reported more protective factors against smoking, such as spending more time in community clubs, higher self-esteem, higher grades, more
parental monitoring, more parent attachment, and more school attachment (Huebner et al., 2005). In this sample, different predictors for smoking were observed across race. For the White female group, grades, perceived parent quality (i.e., “My parents care about me”), and perceived availability of cigarettes were significant predictors of smoking. For the African-American group, attempted suicide, hours spent in club activities, hours spent in sports, and socioeconomic status were all significant predictors of smoking. Three predictors were the same for both groups: coping by taking drugs and frequency of marijuana and alcohol use (Huebner et al., 2006).

Dr. Meszaros and colleagues also conducted focus groups with non-smoking girls in southwest Virginia. Findings from these focus groups showed that these girls received clear messages about the health risks of smoking from parents, peers, and the media (Matheson & Meszaros, 2004). Results from these studies with smokers, former smokers, and non-smokers all draw attention to both the risk and protective factors that should be addressed in smoking intervention programs for adolescent girls in rural areas.

Tobacco use among African-American youth

Concentrating on another distinct population, Dr. Faye Belgrave and Dr. Aashir Nasim at VCU conducted a study on the protective factors against smoking among African American middle school, high school, and college students. Findings indicated that while smoking status increased almost two-fold between middle and high school, a number of cultural and familial factors were protective against smoking, at least in some groups. For example, familial factors (parental support, coping, and monitoring) were protective against smoking status among middle school students, but not high school students. Religiosity was also protective against tobacco use (Nasim, Utsey, Corona & Belgrave, 2006; Nasim, Corona, Belgrave, Utsey, Fallah, 2007). Risk factors for smoking included neighborhood factors (such as drug access), friend use, and risky coping behaviors, more often among middle school students than high school or college students. Drs. Belgrave and Nasim also assessed anti-smoking attitudes, and found that across all groups, anti-smoking attitudes were associated with lower neighborhood crime rates and having fewer friends who use tobacco. Drs. Belgrave and Nasim, along with Dr. Rosalie Corona and other colleagues also examined risk and protective factors among 8th and 10th grade African American students, using statewide survey data collected in 2005. Results showed that low academic
achievement, peer drug use, and early substance use were all predictors of smoking. A protective factor against smoking was being rewarded for prosocial behavior at school (Corona, Turf, Corneille, Belgrave, & Nasim, 2009). Overall, these findings highlight the impact of risk and protective factors on smoking behavior.

Another study by Drs. Belgrave and Nasim focused on how family, contextual, and cultural factors influence smoking among African American adolescents. This study examined elementary, middle, and high school students from urban and rural regions, across several timepoints (after transition to the 6th and 9th grades, as well as after high school). Findings indicated that tobacco use was associated with neighborhood disorganization and stressful events. In contrast, religious support (that is, feeling supported by one’s belief in a higher power) was associated with less tobacco use, and also moderated the negative effects of neighborhood disorganization on tobacco use (Belgrave et al., 2010).

Recently, Dr. Rosalie Corona and colleagues from VCU received a VCU small grant to study communications between African American adolescents and their parents, regarding tobacco use. Results are not yet available.

_Tobacco use among adolescents, across ethnic backgrounds_

Drs. Nasim, Belgrave, & Corona, and colleagues, also examined tobacco use among youth across Virginia, and looked specifically at the relationship between ethnicity (Asian, African-American, White, and Latino) and cigarette use. Findings showed differences between exposure to risks and vulnerability to past 30-day tobacco use, across ethnic groups. Asians-American youth had the lowest exposure to risk factors, but were most likely to report tobacco use. African-American youth had higher exposure to risk factors, but were less likely to report tobacco use. The authors conclude that culture-specific interventions, or interventions with modules that address culture, may be useful for prevention (Nasim, Berry, Belgrave, Corona, & Turf, 2011).

Additional work by Drs. Nasim and Corona focused on reported exposure to anti-smoking messages among African American, Latino, and White youth across the state of Virginia. Ethnicity was related to reported exposure to anti-smoking messages and intention to smoke; the strongest association between exposure to anti-smoking messages and reduced intention to smoke was among African American youth who had never smoked (Nasim &
Corona, 2008).

_Tobacco use among adolescents with behavioral health disorders_

Another distinct population that has been the focus of study is adolescents with psychiatric disorders. In particular, adolescents with Attention Deficit/Hyperactivity Disorder (ADHD) may be more vulnerable to becoming smokers, and are also more likely to have deficits in social skills and behaviors which could increase their vulnerability to smoking initiation. Dr. Zewelanji Serpell (Virginia State University; VSU—Dr. Serpell is now at VCU) and colleagues at JMU used a number of measures to study middle and high school students with ADHD. Results indicated that adolescents with higher social impairment scores were more likely to believe that smoking would help with social interaction and would also enhance mood, reduce boredom, and improve concentration and attention. In addition, adolescents with higher social impairment scores were more likely to have positive attitudes about smoking, and were more likely to anticipate that their peers would accept smoking. Also, students who reported having tried smoking, reported acceptance of smoking among same-aged youths and expressed intentions to smoke in the next 30 days.

In this study, smoking rates increased from middle to high school, and high school students reported increased participation in delinquency among their peers, and that delinquency was associated with smoking. Finally, adolescents who had tried smoking were more likely to report spending more time with friends and having friends who were either smokers and/or supportive of smoking. In total, these findings suggest that among youth with ADHD, several risk factors may make them more vulnerable to becoming smokers, such as fewer social skills and increased delinquency among peer groups. Smoking interventions that target adolescents with ADHD should address these factors.

At VCU, Dr. Julie Linker also studied adolescents with emotional and behavioral disorders. Participants and one of their parents completed questionnaires which asked about smoking behaviors and attitudes, as well as psychological, social, behavioral, and family information. Eight of the 38 adolescents reported smoking “at least a puff” in their lifetimes, and four had smoked daily for at least 1 month. In contrast, no parents reported that their child had smoked, and indicated disapproval of adolescent smoking, although most of the adolescents reported living with a family member who smoked.
In another study focused on adolescents with behavioral health disorders, Dr. J. Randy Koch and Dr. Alison Breland from VCU, along with Dr. Jessica Irons from JMU looked at tobacco use in this population. Literature suggests that high rates of smoking exist in this population, and this research seeks to examine whether or not youth are screened for tobacco use, the prevalence of tobacco use, as well as whether or not tobacco use is addressed by providers. Data collected from chart reviews at four publically-funded, Virginia behavioral healthcare agencies showed that 34% of adolescents were screened for tobacco use. Of those that were screened and used tobacco, only 6% were treated for tobacco use. Further analysis of data from one of the behavioral healthcare agencies studied (where nearly all the clients were African-American) showed that rates of daily tobacco use in this group were much higher than statewide and national prevalence rates (18% in the charts reviewed, vs 2-3% for statewide and national rates; Breland, Nasim, Irons, & Koch, 2013).

Drs. Koch, Breland, and Irons also designed a study to determine the organizational policies and practices for the screening and treatment of both adolescent and adult tobacco use/nicotine dependence, including barriers to screening and treatment, among the network of public, community-based behavioral healthcare services in Virginia (i.e., community services boards). Findings from a behavioral healthcare staff survey suggest that while staff are generally supportive of providing tobacco cessation services, most staff do not currently do this with great frequency. It appears that this may be the result of a lack of training and the lack of clear guidance/policies supporting the delivery of tobacco cessation services.

**Tobacco use among sexual minority adolescents**

At Virginia Tech, Dr. Christine Kaestle recently received a VYTP small grant to study smoking initiation among sexual minority and multiple minority adolescents, and what factors may protect these adolescents from smoking. She will use data from the National Longitudinal Study of Adolescent Health (Add Health) to explore these questions. Preliminary results indicate that sexual minority adolescents experience substantive smoking disparities. Examination of potential protective factors that may ameliorate this disadvantage are ongoing.

These studies with distinct populations provide important prevalence data, and also offer insight into particular risk and protective factors associated with different groups. Prevalence data from several studies indicate that smoking rates increase from middle to high school.
Adolescents in rural areas are more likely to smoke than those in urban areas, and in rural areas, White adolescent females have the highest prevalence rates. Youth who are being treated for behavioral health disorders are at higher risk for tobacco use, although screening and treatment (and related training) may be limited. Several risk and protective factors were identified for adolescents from a variety of ethnic/racial backgrounds, for rural adolescent females, and for adolescents with ADHD. Knowledge of both risk and protective factors could be used to tailor interventions for particular groups, and a more comprehensive understanding of protective factors could be applied to interventions for any population.

**Research on Interventions for the Prevention of Nicotine Dependence**

*Gender-specific interventions*

Designing intervention studies can begin with determining experts’ consensus opinions about what strategies might work best. In an effort to better understand the best smoking prevention practices for female adolescents, Dr. Meszaros and colleagues conducted a multi-wave Delphi study with 14 knowledgeable substance abuse professionals. Results indicated that panelists agreed with some of the relevant literature, including the importance of weight control issues and parental involvement. However, panelists also believed that many methods were equally effective for both males and females, even though they acknowledged differential risk factors for females and the need for prevention programming around these risk factors. These researchers concluded that more research on gender-specific programming is needed before prevention experts are ready to agree on clear and specific practices for adolescent females (Davis et al., 2004). Dr. Meszaros and colleagues also conducted a literature review of prevention and cessation programs for adolescent females, and found few published articles that reviewed effective programs in this area. Further, they outlined approaches that are important for gender-specific programs, as well as the methodology to measure the efficacy of programs (Meszaros et al., 2004).

**Interventions for adolescents with behavioral health disorders**

Dr. Meszaros and colleagues (Steve Evans, Randy Koch, Brian Meyer, and Sheryl Moore) also conducted an exploratory study of service provider experience with adolescent
smoking prevention. The team developed and pilot tested a survey to assess elements of an effective prevention program for youth with psychiatric disorders and to garner advice from service providers who see these youth in their programs. Results indicated that most mental health clinicians believed that adolescents with mental health problems were likely to use tobacco, alcohol and marijuana, but that few reported using a research-based assessment tool or program. Dr. Meszaros and her team subsequently convened a diverse group of stakeholders (including parents, youth, mental health providers and prevention specialists) to select an appropriate prevention program. The Strengthening Families Program (SFP) was selected as a substance abuse prevention tool for this vulnerable population. The researchers conducted a pilot study to assess its effectiveness in preventing tobacco use in adolescents with psychiatric disorders. Twenty-two families from rural and urban areas in Virginia participated in the study. The results of this study indicated that recruiting families for the program and maintaining their participation was feasible, although few significant differences were observed on pre and post program measures. Program modifications have been identified that may enhance the effectiveness of the intervention for this population.

Drs. Steven Evans and Zewelanji Serpell at JMU also focused on a vulnerable population of adolescents—those with Attention Deficit/Hyperactivity Disorder (ADHD). As described earlier, adolescents with ADHD are more likely to be smokers than those without ADHD, and several symptoms of ADHD may be linked to increased smoking behavior. Dr. Evans and his team first developed a middle-school-based, comprehensive model for treating youth with ADHD (Evans, Green, & Serpell, 2005, Evans et al., 2006), and then implemented the program. Results showed significantly decreased parent ratings of inattention for participants in the treatment group; however, these effects disappeared one year following treatment (Evans, Serpell, Shultz, & Pastor, 2007). More encouraging was the finding that one year following treatment, program participants were less likely to try tobacco, although the overall sample size was very small. These findings indicate that comprehensive treatment for ADHD may reduce the risk of tobacco use, but that effects may not last after the program is discontinued.

In addition, Dr. Lori Keyser-Marcus and colleagues from Virginia Commonwealth University conducted a study with the initial goal of determining if a computerized, brief motivational intervention, combined with incentives, could reduce rates of smoking among adolescents being treated for substance abuse. While recruitment for this study proved to be
extremely difficult, Dr. Keyser-Marcus was able to screen 317 participants and enroll 28 smokers. Among the 28 adolescent smokers enrolled, most lived with a smoker (71%), thought smoking was harmful to their health (79% said “definitely”). About a third were willing to give quitting smoking a try (36%), and 21% were willing to cut down on their tobacco use, indicating that these youth may be willing to change their tobacco use behavior. Unfortunately, the researchers were not able to determine the effects of the brief computerized motivational intervention, as too few participants completed the study.

Finally, Dr. Michael Mason and colleagues from Virginia Commonwealth University were funded (for 2012 – 2015) to test a text-messaging based intervention designed to interrupt tobacco use among adolescents who have other substance abuse issues. Dr. Mason and his team will also examine the relationship between adolescent participants’ locations (via GPS) and tobacco-selling outlets. As this study is currently enrolling participants, no data are yet available.

*Other prevention programs*

Six other interventions for adolescents have been studied, or are in development, by VFHY-funded researchers. First, Dr. Steve Danish and Dr. Earl Dowdy, from Virginia Commonwealth University were funded to form a collaborative group to create and test a tobacco-use prevention and healthy eating program for public schools students in Virginia. The researchers brought a collaborative group together, developed a program, and pilot tested the program in two school districts, with 884 students in total (320 students received the intervention). Although no significant differences were observed between the intervention and control groups on measures of tobacco use or eating behavior, there were some promising findings. Students at the intervention schools had a greater reduction in tobacco use prevalence, compared to students at the control schools. Students at the intervention schools were also more likely to increase their consumption of fruits/vegetables (as measured by the percent of students who reported eating five or more servings a day), compared to students at the control schools.

Second, Drs. Haller, Eissenberg, Ingersoll and Heckman piloted a brief intervention (one session of motivational interviewing) to prevent greater nicotine dependence in adolescents with currently low levels of nicotine dependence (other findings described in the “Human Laboratory Studies” section). After the brief intervention, follow-up data was collected at 1, 3 and 6 months
after the intervention. No significant differences between the treatment and control groups were observed, but for both groups, saliva cotinine (a measure of nicotine exposure) and self-reported cigarettes per day decreased.

Third, Drs. Christine Kaestle and Yvonne Chen from Virginia Tech conducted a study on a tobacco media literacy program among rural middle school students. Teaching youth to be media-literate involves helping them understand how the tobacco industry markets to youth and learning how to analyze and evaluate tobacco product advertisements (for example, what tools of persuasion are being used). Drs. Kaestle and Chen have conducted a pilot assessment of their program, and quantitative results show that participants in the treatment group had better general media literacy and some aspects of tobacco-specific media literacy. Other results showed that other tobacco-specific measures of media literacy were not significantly different between the treatment and control groups (Kaestle, Chen, Estabrooks, Zoellner, & Bigby, 2013). A qualitative assessment of the program revealed that participants demonstrated awareness of the persuasive tools advertisers used, and distrust of the tobacco industry, among other themes. Participants also expressed enthusiasm for media production, and excitement about sharing new learning with family members (Chen, Kaestle, Estabrooks, & Zoellner, 2013).

Fourth, as smoking is particularly harmful to medically at-risk youth, Drs. Mary O’Laughlen and Patricia Hollen at the University of Virginia School of Nursing conducted a study targeting adolescents, ages 14-19 years, with asthma. The goal of the study was to determine if a prevention program (that uses cognitive behavioral training and that is primarily online), can improve decision-making processes and increase resistance to tobacco use in adolescents with asthma. The intent was to provide information related to the interaction of asthma medications and substance use by health professionals as a means of helping adolescents make difficult choices in typical social situations. Adolescent decision-making, substance use motivation, and substance use behavior were assessed at 6-months (immediate effect) and 12-months (sustained effect) post-intervention. Ninety participants were enrolled at 2 sites: UVA and VCU. Participants provided very positive feedback about the intervention. At the 6-month follow-up, no significant differences were observed between groups, but a measure of risk motivation decreased, and this approached significance. Overall, attrition of those participants was a major problem for the study, and only 54% stayed in the study for 12 months, limiting data analysis.
Fifth, Drs. Kulbok and Meszaros conducted a study that brought together university researchers with youth and parents in a southern rural county, in an effort to design and test a drug use prevention program model. First, these researchers created a community participatory research team, comprised of youth, parents, community leaders, as well as university researchers. Second, this group conducted a community assessment to determine what factors influence substance use and non-use in this area, in order to select an appropriate prevention program. Preliminary decisions made by the community participatory research team were that the program should target middle aged adolescents, should be conducted within the summer 4-H camp, and should be conducted by high school students and 4-H camp counselors (Kulbok, Thatcher, Park, & Meszaros, 2012).

Finally, Dr. Rosalie Corona and colleagues from VCU are working to evaluate two evidence-based parenting programs (Family Check Up and Staying Connected with Your Teen), in terms of their effect on preventing youth tobacco use among a high-risk group of youth (youth who are truant). As this study is currently enrolling participants, no data are yet available.

Overall, these studies show that progress has been made with the development and implementation of effective interventions for the prevention and/or reduction of adolescent tobacco use. For example, exploratory studies show that substance abuse professionals acknowledge the need for more information about gender-specific programming, and that more research-based prevention programs for adolescents with psychiatric disorders are needed. Also, recent work has shown that researchers and community members can effectively collaborate to design a drug use prevention program. Several researchers reported results from interventions, with mixed findings. Results from one intervention for youth with ADHD showed reductions in parent ratings of inattention and a reduced likelihood to try smoking. Results from another study showed that youth can learn how to become media-literate when interpreting tobacco advertisements, a potentially effective prevention technique. However, results from a brief intervention for adolescents with low nicotine dependence did not find significant reductions in smoking between experimental and control groups. Results from another study revealed no differences on measures of tobacco use between the intervention and control groups, after exposure to a tobacco prevention program. Finally, results from an intervention for adolescents with asthma also showed no differences between the intervention and control groups, although some measures did approach significance. Clearly, further work in this area is needed to develop
effective youth tobacco use prevention programs, and to surmount difficulties with recruitment and retention of youth participants.

**Research on Tobacco Policy and Anti-Smoking Campaigns**

Changing policies and/or laws surrounding access to tobacco can also reduce use and dependence among adolescents. At the University of Virginia, Richard Bonnie, LLB, has been involved in a number of activities to better understand the impact of policies and laws surrounding tobacco use. First, Mr. Bonnie created a Working Group on Youth-Centered Tobacco Policy Research, with the goal of creating an active research program of policy-related empirical studies relating to tobacco addiction among youth. Second, Mr. Bonnie and his team also conducted several tobacco control studies, such as a review of retail-establishment compliance checks, a review of enforcement of the Master Settlement Agreement, reviews that contributed to a recent Institute of Medicine report on tobacco, and a study of youths’ reactions to counter-advertising. Mr. Bonnie has also completed some more recent work on issues surrounding tobacco use in multi-unit dwellings. Each activity is described in further detail below.

Using data obtained from the Department of Behavioral Health and Developmental Services (DBHDS) and the Virginia Department of Alcoholic Beverage Control (ABC), Mr. Bonnie and colleagues analyzed data for retail-establishment, no-sales-to-minors compliance checks in Virginia. Results indicated that the non-compliance rate declined from 9.73% (2002-03) and 9.85% (2003-04) to 9.03% (2004-05), but that there was a significant jurisdictional variation in compliance. More specifically, among jurisdictions with at least 250 outlets, the rate of noncompliance ranged from low (4.4% in Roanoke; 7.5% in Prince William County) to high (12.4% in Fairfax County; 16.9% in Chesterfield County). A significant variation in non-compliance among types of retailers was also observed (15.5% in drug stores; 9.9% in convenience stores; 8.5% in groceries/supermarkets; 4.5% in restaurants).

The researchers also analyzed whether or not store clerks asked purchasers of tobacco products their age or checked their IDs and whether or not this varied by the type of outlet and the race/ethnicity of the purchaser and clerk. Of the total attempted purchases, clerks did not check the purchaser’s age in 22.41% of cases. Of the sales made, clerks did not check the purchaser’s age in 33.62% of cases. Sales practices did not differ according to type of outlet, but
the likelihood of a successful purchase by an underage buyer was related to gender and
race/ethnicity of the purchaser and clerk—sales were most likely when a female buyer attempted
to purchase tobacco from a female clerk, and sales were least likely when a male buyer
attempted to purchase tobacco from a male clerk. Also, Black purchasers were more likely to
successfully purchase tobacco and more likely to sell tobacco than Whites, and Hispanics were
more likely to successfully purchase tobacco and more likely to sell tobacco than non-Hispanics.

Mr. Bonnie and his colleagues also surveyed store managers and clerks—both reported
knowledge of the law, although they generally overestimated the penalties associated with
violation. In addition, both managers and clerks generally reported favorable attitudes toward
the law and community support for the law. They also indicated awareness of periodic
compliance checks, and did not perceive that their businesses were economically disadvantaged
by compliance. Although this study could not provide a direct measure of compliance by these
particular respondents, they did report having been found in compliance during past checks.
Unfortunately, owners and managers of these tobacco retail outlets did not appear to have
adopted in-store policies and practices designed to reduce non-compliance, such as policies
requiring clerks to check IDs and conducting their own monitoring of sales.

Mr. Bonnie and his team also reviewed the National Association of Attorneys General’s
(NAAG) enforcement of the MSA, by examining several court cases, and outlined the
difficulties and successes observed in enforcing the MSA. In addition, his team reviewed the
variety of current restrictions for shipments of alcoholic beverages, as tobacco use among
adolescents could be reduced by restricting online sales and direct shipment of tobacco products
to individuals. For example, many states restrict shipping to licensed wholesale or retail outlets,
and prohibit direct shipping of alcohol to individuals. Conclusions from this review included
that a better understanding of the regulations for shipping alcoholic beverages provides a
precedent for tobacco shipments, and that legislation in this area should be explored (Kinney,
2007).

Mr. Bonnie’s team also reviewed industry-sponsored youth education programs, and
concluded that many of these anti-tobacco campaigns are ineffective and possibly disguised
marketing schemes. For example, many industry anti-tobacco campaigns use weak messages
(i.e., Philip Morris’ “Think. Don’t Smoke” campaign), and some research has found that youths
who view Philip Morris ads are more likely to report a future intention to smoke. In a similar
vein, Marian Moore, Erin Sutfin, and Lisa Szykman examined high school students’ reactions to several types of anti-tobacco advertisements. Results indicated that exposure to ads depicting “negative life circumstances” (smoking as grotesque, unattractive) were associated with decreased intention to smoke, compared to those showing “industry manipulation” (tobacco companies denying the addictive nature of tobacco, and targeting adolescents) and control advertisements. Also, participants who were smokers disliked all the anti-tobacco advertisements more than participants who were not smokers (Sutfin, Szykman, & Moore, 2008).

More recently, Mr. Bonnie and his colleagues have conducted research on tobacco use and attitudes among property managers that manage or own multi-unit dwellings across Virginia (specifically, in Alexandria, Richmond, Roanoke, and Norfolk). Overall, property managers reported that about 37% of their tenants smoke cigarettes, and 33.8% reported having a formal nonsmoking policy. Of those property managers that had a formal nonsmoking policy, approximately half (53.4%) reported that their tenants or tenants’ guests had violated that policy. Most respondents did not have any formal policy, and reported little interest in implementing a nonsmoking policy, indicating that such policies were very difficult to enforce. These respondents also perceived little demand for nonsmoking policies among their tenants and potential tenants, and most (72.1%) did not believe that exposure to second-hand smoke was a significant health concern for their tenants. The authors concluded that youth living in multi-unit dwellings are likely to be exposed to secondhand smoke, and an environment where adults smoke may increase youths’ beliefs that smoking behavior is normative, thus increasing the likelihood that they will begin smoking.

Finally, Dr. Alan Dow and colleagues at VCU explored the extent to which students at Virginia medical and dental schools are trained on tobacco cessation. Dr. Dow and his team conducted structured interviews with education leaders at four Virginia medical schools and one dental school that were responsible for tobacco cessation education, and asked about the instruction and assessment methods used. Findings from this study showed that, in general, students are taught about the epidemiology of smoking and the health effects of smoking, as well as the importance of asking every patient if they smoke. However, gaps exist in teaching students how to actually diagnose and treat patients, that is, referring patients to quit smoking resources, creating quit plans, prescribing pharmacotherapy, and arranging for follow-up. Barriers to including education on actual treatment included cost, curricular time, coordination of
instruction, and faculty development.

Overall, findings from research on tobacco control policies indicate that retailers vary in their compliance with no-sales-to-minors laws, and that successful purchases by underage buyers are related to the gender and race/ethnicity of the purchaser and the clerk. Store managers and clerks did report knowledge of the no-sales-to-minors laws, but they did not all have in-store policies to reduce sales to minors (such as requiring clerks to check IDs). In addition to strengthening no-sales-to-minors policies, sales to adolescents could also be reduced by restricting the shipment of tobacco (i.e., via the internet), by applying existing regulations used in the shipment of alcoholic beverages to tobacco. Also, youth living in multi-unit dwellings may have higher exposure to second-hand smoke, and with few nonsmoking policies, may believe that smoking is normative. Other findings indicate that anti-tobacco campaigns that emphasize the negative life circumstances associated with smoking are associated with a decreased intention to smoke. Finally, research looking at education on tobacco in Virginia’s medical and dental schools shows that while the epidemiology and health consequences of tobacco use are taught, gaps exist in teaching students how to actually treat patients.
Establishment of the Center for the Study of Tobacco Products at VCU

VFHY funding helped lead to a much larger research grant: in 2013, VCU was awarded an $18.3 million grant by the Food and Drug Administration/National Institutes of Health to become one of 14 Tobacco Centers of Regulatory Science, nationwide. The goal of VCU’s Center for the Study of Tobacco Products is to develop and test a model for evaluating modified risk tobacco products (MRTPs) that may come to be regulated by the FDA. An example of a possible future MRTP is electronic cigarettes. The specific aims of the CSTP are: (1) Examine factors that influence MRTP nicotine and toxicant yield, (2) Compare short-term effects of MRTPs to other products in the human laboratory, (3) Characterize effects of real-world MRTP use in the natural environment, and (4) Study the influence of attitudes, beliefs, and cognitions on MRTP use and misuse. Overall, results from these studies will provide information necessary for the sustained success of FDA’s mandate to regulate novel tobacco products.

As research shows that youth are using electronic cigarettes, and this use has been increasing (e.g., CDC, 2013), the goals of the CSTP are related to the goals of the VYTP. The VYTP is now being housed in this new, innovative Center. This will allow for collaborations between the two groups. However, no funding for the VYTP comes from the CSTP.
The VYTP and Student Training

Although the VYTP was not designed to train students in research on youth tobacco use, numerous students have become involved with VYTP and VFHY-funded investigators. Notably, some students affiliated with VYTP and/or VFHY-funded investigators have gone on to successful careers in tobacco research and tobacco regulation. Please note that the below list includes examples only, and that a future report will more fully explore the impact of VFHY/VYTP funds on the careers of both students and junior faculty.

Erin Sutfin was a student of Richard Bonnie’s at the University of Virginia and used VFHY funds to conduct research on tobacco advertising campaigns. Dr. Sutfin is now an Assistant Professor of Social Sciences and Health Policy at Wake Forest School of Medicine, and is a Project Director for another FDA/NIH funded Tobacco Center of Regulatory Science (with investigators at the University of North Carolina). Kia Jackson was a student who worked with Dr. Imad Damaj at VCU, using animal models of nicotine addiction. Dr. Jackson is now a behavioral pharmacologist at the FDA Center for Tobacco Products. Craig McDonald was a student of Dr. Robert Smith at GMU, and worked on several studies looking at the effects of early nicotine exposure, using animal models. Dr. McDonald is now an Assistant Professor of Psychology at GMU and is currently a Co-PI with Dr. Smith on a large VFHY grant. Jennifer Brielmaier was also a student of Dr. Robert Smith at GMU, and worked on studies looking at the effects of stress on nicotine preference, as well as the behavioral effects of nicotine, using animal models. Dr. Brielmaier is now also an Assistant Professor of Psychology at GMU and continues to be involved with nicotine-related research. Victoria Sanchez studied with Dr. Wendy Lynch at UVA, looking at the relationship between exercise and nicotine seeking behavior. Dr. Sanchez went on to a post-doctoral fellowship at the University of Pennsylvania, where she is continuing nicotine-related research. Trenette Clark was a student of Dr. Faye Belgrave’s, and worked on a project looking at stress and tobacco use among African-American adolescents. Dr. Clark is now an Assistant Professor at the University of North Carolina, and recently received a K award from NIDA to study tobacco and other drugs. Anh Nguyen also worked with Dr. Belgrave to examine smoking among African-American adolescents. Dr. Nguyen is now a Cancer Prevention Fellow at the National Cancer Institute, and conducts research on health disparities and cancer screening.
**Conclusions**

Overall, VFHY-funded research studies have encompassed a wide variety of topics related to adolescent tobacco use and prevention. Animal models have provided key findings about the biological effects of nicotine and have identified potential strategies for tobacco cessation in humans, genetics research has identified genes and other risk factors implicated in tobacco use, human laboratory studies have helped characterize the effects of nicotine, and epidemiological studies have described the prevalence of tobacco use, as well as beliefs, attitudes, risk factors, and protective factors related to tobacco use. In addition, several interventions have been developed and tested, and research on policy-related issues has provided useful information about retailer compliance with age restrictions, the effectiveness of anti-tobacco advertisements, suggestions for tobacco shipment restrictions, and training about tobacco at Virginia’s medical and dental schools.

Results from studies on the basic biology of nicotine addiction demonstrate adolescents’ particular vulnerability to tobacco initiation and potential dependence, and the critical effects that nicotine has on brain development and learning, both during adolescence and even earlier (i.e., perinatal exposure). These studies also highlight the detrimental effects of even limited nicotine exposure during adolescence, the effects of concurrent use of nicotine and methylphenidate, and that females may be especially affected by nicotine withdrawal. These preclinical studies suggest that behavioral interventions like exercise might improve tobacco cessation outcomes if implemented in adolescents. Studies of genetics have helped clarify that adolescent vulnerability is likely influenced by several genes whose expression is affected by nicotine exposure during adolescence, and that environmental factors (e.g., family adaptability, cohesion, parental discipline and leadership) may moderate these genetic effects.

Findings from human laboratory studies support results from studies in animals and provide further information. For example, some adolescents smoke very little, yet are still exposed to nicotine, experience its effects, and may smoke to reduce withdrawal symptoms. In addition, adolescent smokers have some cognitive deficits which may indicate disrupted brain function. Studies from the human laboratory also indicate that several variables, such as measures of ADHD, anxiety, family functioning, conduct disorder and schizotypal personality, as well as alteration in brain activity, may also be associated with vulnerability to adolescent
tobacco use.

Epidemiological studies also show how individuals differ with regard to vulnerability to tobacco use. Adolescents with ADHD are more likely to smoke, and in rural Virginia, White female adolescents report the highest prevalence of smoking. Across several groups, smoking prevalence increases from middle to high school. Adolescents with other risk factors are also more likely to smoke (e.g., adolescents who report more delinquency, more depression, greater cigarette and drug access, other drug use, lower socioeconomic status, and more risky coping behaviors). Adolescents may also use tobacco for weight management, and concern about weight could increase adolescents’ use of tobacco. In addition, initial tobacco episodes among novice smokers typically occur at parties or other social situations, often when alcohol is also used. Also, youth who are being treated for behavioral health disorders are at higher risk for tobacco use, although screening and treatment (and related training) may be limited. Other studies have shown that girls may be more likely than boys to obtain cigarettes from friends and adults, that there may be limited access to prevention programs in some communities, and that youth may be obtaining incorrect information about tobacco from the internet.

However, some factors can protect adolescents from smoking, such as greater community, school, and parental involvement, receiving clear messages about the health risks of smoking, and having a religious affiliation. Knowledge of both risk and protective factors could be used to tailor interventions for particular groups, and a more comprehensive understanding of protective factors could be applied to interventions for any population.

VFHY-funded intervention studies have begun to develop or modify interventions to prevent or reduce adolescent tobacco use. For example, targeted interventions (i.e., for adolescent girls, adolescents with ADHD, adolescents with asthma) have been developed, along with other interventions, although results have been mixed. Importantly, creating effective interventions for adolescents, as well as implementing them and measuring their effects have proven to be challenging for many researchers globally (for reviews, see: Grimshaw & Stanton, 2006; Sowden et al., 2003, Thomas & Perera 2006; Thomas et al., 2007). For this reason, continued work to develop and test effective prevention and treatment interventions is critical.

VFHY-funded research has also shown that variation exists in compliance with no-sales-to-minors laws, and that shipping restrictions for tobacco could be enhanced by adapting certain current restrictions for shipping alcoholic beverages. In addition, youth living in multi-unit
dwellings may have higher exposure to second-hand smoke, and with few nonsmoking policies, may believe that smoking is normative. Other findings indicate that some anti-tobacco advertising (specifically, those that depict the negative life circumstances associated with smoking) can also reduce adolescents’ intention to smoke. Finally, work examining Virginia medical and dental schools shows that large gaps exist in training about tobacco treatment. Enforcing compliance with no-sales-to-minors laws, modifying existing tobacco shipment laws, promoting nonsmoking policies in multi-unit housing, increasing use of particular types of anti-tobacco advertising, and changing medical schools’ policies surrounding education on treatment for tobacco use could potentially prevent and reduce adolescent tobacco use.

In summary, findings from VFHY-funded studies indicate that preventing and/or treating tobacco use/dependence in adolescents is complex and must address a variety of issues. An integrated, collaborative approach to prevention and/or treatment will likely result in the most effective methods. Thus far, VFHY-funded researchers have effectively collaborated on a number of projects, across departments, universities and geographic areas. For example, researchers studying nicotine in animals and researchers studying genetics have worked together on several initiatives. Also, researchers from Virginia Tech, VCU, UVA, JMU, and VSU have joined forces on several projects, and investigators have conducted research in various regions of Virginia. This is a unique research model which arose from the vision of the VFHY to support multidisciplinary, multi-institutional research.

The VYTP is also one component of a much larger youth tobacco control effort in Virginia. Of note, VFHY funding helped lead to a much larger research grant: in 2013, VCU was awarded an $18.3 million grant by the Food and Drug Administration/National Institute on Drug Abuse to become one of 14 Tobacco Centers of Regulatory Science, nationwide. The goal of VCU’s Center for the Study of Tobacco Products is to develop and test a model for evaluating modified risk tobacco products (MRTPs) that may come to be regulated by the FDA (such as electronic cigarettes). As research shows that youth are using electronic cigarettes, and this use has been increasing (e.g., CDC, 2013), the goals of the CSTP are related to the goals of the VYTP.

VFHY-funded researchers will likely continue to provide significant contributions to understanding, preventing, and treating tobacco use and dependence in adolescents. Currently, a number of investigators are working on various projects, which will provide a springboard for
additional work on the issues surrounding youth tobacco use. In addition to existing work, even more powerful, innovative work could be accomplished by creating new, unconventional collaborations across departments and universities. Such novel partnerships could more effectively build on existing research; translate research to effective practice, and ultimately, reduce the toll of tobacco use on Virginia’s youth.
Recommendations

This report offers several recommendations for both researchers and the VFHY. For researchers, recommendations include: 1) seek collaborative research partnerships, 2) employ innovative methodologies to study novel tobacco use issues, 3) develop and design prevention intervention studies, and 4) increase external funding among VYTP/VFHY investigators. For the VFHY: 1) establish short and long-term priorities for research, 2) identify specific lines of research that are consistent with VFHY’s mission as priorities for future funding, 3) support statewide tobacco policy change and enforcement, 4) develop a system to track the impact of VFHY funding, and 5) integrate research results into VFHY programming, and 6) continue funding support for the VYTP. Additional details are included below:

Recommendations for researchers:

1. **Seek collaborative research partnerships to address gaps in program priorities and the need for greater research translation.** Collaborative research partnerships should be increased in order to expand our research capacity, address novel research topics and improve research translation. A number of shared interests already exist among VYTP researchers from diverse disciplinary backgrounds. For example, a number of VYTP-funded researchers have measured risk and protective factors (perinatal exposure, genetic, environmental, social, familial, and psychiatric factors) for youth tobacco use. Intentionally linking these researchers with tobacco prevention specialists from community- and school-based programs might accelerate the translation of important survey findings into effective prevention interventions for youth. Ultimately, such collaborations could foster a more active research to practice effort.

2. **Employ innovative methodologies to study novel tobacco use issues.** Youth are exposed to a variety of new and/or increasingly popular tobacco products (e.g., products that are not cigarettes: electronic cigarettes, smokeless tobacco, little cigars) and novel ways to use these products. In addition, during the past decade, the tobacco industry has developed more sophisticated marketing and advertising strategies that target youth (e.g., social media). Researchers should develop innovative methods to study youth tobacco
use and contexts which promote use. Such methods might include social network analysis and social media analysis.

3. *Develop and design prevention intervention studies.* VFHY-funded researchers have conducted several intervention studies, and these have provided important information about potential strategies to prevent or reduce tobacco use among specific groups of adolescents. However, a gap exists in this area, particularly in the translation of research findings to effective interventions. Importantly, many tobacco researchers have found that creating well-designed interventions, implementing them, and measuring results for this population is challenging, and only a few interventions have consistently been proven effective. As outlined in recommendation #1, collaboration research partnerships might be used to increase the number of effective interventions available, as well as the implementation and dissemination of those interventions for the prevention and treatment of youth tobacco use. Innovative methods to study youth tobacco use (as described in recommendation #2) might lead to innovative interventions. We note that the most recent RFP for VFHY funding included prevention trials as a possible research area.

In addition, the creation and development of a prevention trials network could help identify collaborations between researchers and practitioners. Through these collaborations, researchers and practitioners could use community-based settings to develop, implement and test prevention programs and interventions, as well as disseminate information and promote effective programs.

4. *Increase external funding among VYTP/VFHY investigators.* The VYTP is one component of a much larger youth tobacco control effort in Virginia. Between FY 2007 and FY 2013, VYTP members made 100 applications to federal, state, and private organizations other than VFHY, and 49 were funded (49% of all applications submitted). In addition, VFHY funding helped lead to a much larger research grant: in 2013, VCU was awarded an 18.3 million grant by the Food and Drug Administration/National Institute on Drug Abuse to become one of 14 Tobacco Centers of Regulatory Science, nationwide. The goal of VCU’s Center for the Study of Tobacco Products is to develop...
and test a model for evaluating modified risk tobacco products (MRTPs) that may come to be regulated by the FDA.

Researchers are encouraged to continue to apply to outside sources for funds to study tobacco in general. Further, success might be increased by using collaborative and/or novel methods, as described in recommendations #1 and #2. Support for collaborative and/or novel drug abuse research currently exists at the federal level, based on several current funding announcements. For example, funding exists for multidisciplinary translation and implementation of evidence-based prevention and treatment research, collaborations across researchers in areas such as neuroscience, cognition, psychology, and economics to study substance abuse, collaborations across researchers studying genetics, and collaborations for international tobacco research. Numerous funding announcements also exist for novel approaches to the prevention and treatment of substance abuse.

**Recommendations for VFHY:**

1. *Establish short and long-term priorities for research.* With the assistance of the VYTP, VFHY should review past and current funded research and assess how these studies match the goals and priorities of the VFHY. Information gleaned from this review could help to determine short and long-term priorities for future VFHY funded research.

2. *Identify specific lines of research that are consistent with VFHY’s mission as priorities for future funding.* Based on the findings summarized in this report, several areas of research hold promise for additional important findings and potentially for NIH funding. For example, research described here has helped to elucidate the biological underpinnings of nicotine addiction and the relationship between genetic and environmental factors. A more complete understanding in these areas could guide effective intervention efforts by identifying specific therapies for individuals in particular groups (i.e., based on gender, age, perinatal nicotine exposure, or specific genetic variations), and proposals could be requested to address specific research questions such as these. In addition, further VFHY support in the basic biology and genetics of nicotine addiction could help researchers
obtain NIH funding. Currently, NIDA has several relevant funding announcements, including those that address the processes and mechanisms underlying drug abuse, the relationships between genetic and environmental factors, and the differential response among genetically vulnerable subgroups.

VFHY-funded epidemiological research has revealed information on smoking prevalence as well as risk and protective factors associated with smoking. These findings could also help direct effective intervention efforts for specific groups or regions (e.g., adolescent girls, or adolescents in southwestern Virginia), as well as the factors effective interventions might address (e.g., the home environment and parental support, concerns about weight, psychiatric issues). Support for epidemiological research in this area also exists at the federal level; several funding announcements highlight the importance of continued research to understand the nature, extent, consequences, and etiology of drug abuse across various groups.

VFHY-funded policy-related studies have provided important information about sales to underage buyers, anti-tobacco advertising, and tobacco education at Virginia’s medical schools. Future policy-related studies should continue to address the impact of policy decisions on youth tobacco use, especially over time and if tobacco control policies change. Additional policy-related studies could explore the effects of tobacco indemnification on youth tobacco use, the relationship between MSA funding and youth tobacco use across different states, the impact of restaurant smoking bans on adolescent and young adult staff health and attitudes, the effect of any future electronic cigarette policy changes on youth use, and the effect of any changes to tobacco education at medical schools.

Finally, VFHY-funded researchers have conducted several studies on tobacco use among youth with psychiatric disorders. Additional work in this area is warranted, given that adults with mental health/substance abuse disorders account for over 40% of all cigarettes used in the US (Lasser, Boyd, Woolhandler, Himmelstein, McCormick, & Bor, 2000). This work could include basic research, epidemiological studies, prevention trials, and/or
work with organizations to increase screening and treatment.

3. **Support statewide tobacco policy change and enforcement.** VFHY is encouraged to continue their current support of evidence-based policy changes that further reduce youth tobacco access and use and encourage stronger enforcement of existing tobacco control laws affecting youth.

4. **Develop a system to track the impact of VFHY funding.** VFHY-funded researchers have applied for and received additional funds from outside organizations. The combination of VFHY funding and external funding has led to a tremendous amount of tobacco research being conducted by current and former VYTP investigators. A mechanism should be established to track and report those investigators’ work in order to provide a truly comprehensive picture of the impact of VFHY funding on youth tobacco research in Virginia, and nationally. This could be accomplished by locating all current and former VFHY-funded investigators, and developing a survey or structured interview to be conducted with these investigators.

5. **Integrate research results in VFHY programming.** The VFHY might look for more ways to bring relevant findings into the prevention programming they fund. For example, findings from this report show the developmental impact of nicotine exposure, and also show the need to have targeted prevention programming based on different risk factors in different subpopulations.

6. **Continue funding support for the VYTP.** The VYTP has been successful in the formation of a unique statewide network of multidisciplinary, multi-institutional tobacco scientists, who are focusing on adolescent tobacco use. The VYTP Research Coalition is the ideal mechanism to facilitate the promotion and implementation of research on youth tobacco issues. Further, the VYTP Research Coalition is uniquely positioned to support the implementation of the above recommendations.
Appendices
## VFHY-funded Grants

<table>
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<tr>
<th>PI Name and Institution</th>
<th>Award Period (Fiscal Year)</th>
<th>Project Name/Focus</th>
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<tbody>
<tr>
<td>Robert Balster, PhD</td>
<td>2006-2009</td>
<td>Research Coalition Core/Virginia Youth Tobacco Projects</td>
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<td>J. Randy Koch, Ph.D.</td>
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<tr>
<td>Robert Barnet, PhD</td>
<td>2006-2009</td>
<td>Long-Term Impact of Adolescent Nicotine on Cognitive Function</td>
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<tr>
<td>Joshua A. Burk, PhD</td>
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<td>Pamela Hunt, PhD</td>
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<td>The College of William &amp; Mary</td>
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<tr>
<td>Faye C. Belgrave, PhD</td>
<td>2002-2006</td>
<td>Pathways to Smoking Among African-American Adolescents: Family, Contextual, and Cultural Factors</td>
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<td>Faye Belgrave, PhD</td>
<td>2003-2004 VYTP Small Grants</td>
<td>Protective Factors for Tobacco and Other Drug Use Among African American Adolescents</td>
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<td>Warren Bickel, PhD</td>
<td>2013-2014 VYTP Small Grants</td>
<td>The Consequences of Self-Control Failure in Adolescent Smokers</td>
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<td>Virginia Tech</td>
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<td>PI Name and Institution</td>
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</table>
| Richard J. Bonnie, LLB The University of Virginia | 2002-2006 | 1. Working Group on Youth-Centered Tobacco Policy Research  
2. Retailer Compliance Study  
3. Enforcement of the Tobacco Master Settlement Agreement: A New Paradigm?  
4. The Role of Emotion in Youths’ Reactions to Tobacco Counter-Advertising  
5. State statutes governing direct shipment of alcoholic beverages to consumers: precedents for regulating tobacco retail shipments |
<p>| Richard Bonnie, JD Shelly Jackson University of Virginia | 2007-2008 VYTP Small Grants | Modifying Social Norms as a Policy Tool for Preventing Youth Smoking Initiative: A Proposal for Monitoring Changes in Nonsmoking Policies in Multiunit Dwellings in Virginia |
| Darlene J. Brunzell, PhD Wendy J. Lynch, PhD Virginia Commonwealth University | 2009-2012 | Exercise as a Prevention and Intervention Strategy for Nicotine Use in Adolescents |
| Darlene J. Brunzell, PhD Wendy J. Lynch, PhD Virginia Commonwealth University | 2012-2015 | Exercise and Environmental Enrichment to Prevent Nicotine Addiction in Adolescent Males and Females |
| Joshua Burk, PhD The College of William and Mary | 2003-2004 VYTP Small Grants | Adolescent Nicotine and Alcohol Administration and Cognition |
| Rosalie Corona, PhD Virginia Commonwealth University | 2012-2015 | Can Parents Help Prevent Youth Tobacco Use? An Evaluation of Two Evidence-based Parenting Programs |
| Rosalie Corona, PhD Virginia Commonwealth University | 2013-2014 VYTP Small Grants | African American Parent-Adolescent Communication About Tobacco Use |</p>
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<tr>
<td>Imad Damaj, PhD</td>
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<td>Early Nicotine Exposure and Vulnerability to Drug Abuse</td>
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<td>Steve Danish, PhD Early Dowdy, PhD</td>
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<td>LIFT+: Assessing the Efficacy of a School-Based Health Promotion Intervention on Tobacco Use and Fruit and Vegetable Consumption among Rural Youth LIFT+ program</td>
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<td>Virginia Commonwealth University</td>
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<td>Bruce Dembling, PhD University of Virginia</td>
<td>2003-2004 VYTP Small Grants</td>
<td>Youth Tobacco Control Policy Research: Behavioral and Biological Factors</td>
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<td>Early Dowdy, PhD Virginia Commonwealth University</td>
<td>2009-2012</td>
<td>Tobacco Use Prevention and Health Promotion in Rural Virginia Schools: Translating Research into an Evidence-Based Model Curriculum</td>
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<td>Elizabeth A. Fries, PhD Diane Baer Wilson, EdD, RD Virginia Commonwealth University</td>
<td>2002-2006</td>
<td>Youth Tobacco Evaluation Project</td>
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<td>Karl J. Fryxell, PhD George Mason University</td>
<td>2007-2008 VYTP Small Grants</td>
<td>A Targeted Molecular and Genetic Analysis of the Effects of Nicotine Exposure on Previously Unexposed Adolescents</td>
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<td>Karl J. Fryxell, PhD George Mason University</td>
<td>2010-2011 VYTP Small Grants</td>
<td>Which signaling pathway(s) drive nicotine preference in adolescent C57BL/6J mice?</td>
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<td>Karl J. Fryxell, PhD</td>
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<td>What Social and Molecular Factors Drive Nicotine Preference in Adolescent Mice?</td>
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<td>Deborah L. Haller, PhD</td>
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<td>Preventing Addiction in Adolescent Smokers</td>
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<td>Thomas E. Eissenberg, PhD</td>
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<td>Karen Ingersoll, PhD</td>
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<td>Carolyn Heckman, PhD</td>
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<td>Alison Brelan, PhD</td>
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<td>Nadine Kabbani, PhD</td>
<td>2013-2014 VYTP Small Grants</td>
<td>Molecular Mechanisms Underlying Menthol Cigarette Addiction</td>
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<td>Christine Kaestle, PhD</td>
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<td>Predicting Patterns of Tobacco Use among Virginia Youth: Untangling the Interplay of Gender, Race, Age, Health Beliefs, Social Environments and Prevention</td>
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<td>Christine Kaestle, PhD</td>
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<td>Media Literacy Tobacco Prevention for Youth in Virginia: A Randomized Impact Assessment Pilot Study</td>
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<td>Yi-Chun Chen, PhD</td>
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<td>Virginia Polytechnic Institute &amp; State University</td>
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<td>Christine Kaestle, PhD</td>
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<td>Protective Factors against Smoking Initiation for Sexual Minority and Multiple Minority Adolescents</td>
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</table>
| Kenneth S. Kendler, MD  | 2002-2006                 | 1. The Role of Genetic, Family Environmental, and Individual-Specific Environmental Risk Factors in the Etiology of Tobacco Initiation and the Progression to Nicotine Dependence  
<pre><code>                       |                           | 2. Molecular Genetic Identification of Individual Genes that Influence Vulnerability to Tobacco Initiation and the Progression to Nicotine Dependence |
</code></pre>
<p>| Virginia Commonwealth University |                   |                   |
| L. Keyser-Marcus, PhD  | 2010-2011 VYTP Small Grants | Clearing the Air: Computerized Screening and Brief Intervention for Teen Smoking |
| J. Kienzle, PhD        |                           |                   |
| R. Pickens, PhD        |                           |                   |
| Virginia Commonwealth University |                   |                   |
| Randy J. Koch, PhD     | 2009-2012                 | Tobacco Use among Youth Receiving Public Behavioral Healthcare Services |
| Alison Breland, PhD    |                           |                   |
| Jessica Irons          |                           |                   |
| Virginia Commonwealth University |                   |                   |
| Pamela Kulbok, PhD     | 2003-2004 VYTP Small Grants | Protective Factors and Youth Nonsmoking Behavior |
| University of Virginia |                           |                   |
| Pamela Kulbok, PhD     | 2009-2012                 | Partnering with Rural Youth and Parents to Design and Test a Tobacco, Alcohol and Drug Use Prevention Program Model |
| Peggy Meszaros, PhD    |                           |                   |
| University of Virginia |                           |                   |
| Julie Linker, PhD      | 2003-2004 VYTP Small Grants | Smoking Habits of Adolescent Outpatients with Emotional and Behavioral Disorders |
| Virginia Commonwealth University |                   |                   |</p>
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<td><strong>Wendy J. Lynch, PhD</strong>&lt;br&gt;University of Virginia</td>
<td>2007-2008 VYTP Small Grants</td>
<td>Factors Predictive of Vulnerability to Nicotine Addiction during the Transition from Adolescence to Adulthood: An Animal Model</td>
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</tbody>
</table>
| **Billy R. Martin, PhD**<br>Virginia Commonwealth University | 2002-2006 | 1. Gene Microarray Analysis of Nicotine Effects on Brain Tissue  
2. Nicotine Metabolism and Pharmacokinetics  
3. Acute Behavioral Effects of Nicotine Administration in Adolescent Mice  
4. Effects of Prenatal Exposure to Nicotine on Vulnerability to Addiction  
5. Nicotine Self-Administration and Place Preference Behavior in Rats |
| **Billy Martin, PhD**<br>Kenneth S. Kendler, PhD<br>Imad Damaj, PhD<br>Michael Miles, PhD<br>Virginia Commonwealth University | 2007-2009 | 1. Establishing an association between stress/anxiety and rewarding properties of nicotine in mice  
2. Determine behavioral quantitative trait loci for nicotine CPP and identify candidate gene expression networks correlated with nicotine CPP by expression profiling  
3. The genetics of smoking initiation and nicotine dependence in humans: statistical and molecular approaches |
<p>| <strong>Michael Mason, PhD</strong>&lt;br&gt;Virginia Commonwealth University | 2012-2015 | Reducing Teen Tobacco Use Via Text Messaging: Motivational Interviewing Integrated with Social Network Counseling |
| <strong>Craig G. McDonald</strong>&lt;br&gt;George Mason University | 2010-2011 VYTP Small Grants | An electrophysiological study of neurocognitive functioning in adolescent smokers |
| <strong>Peggy S. Meszaros, PhD</strong>&lt;br&gt;Virginia Polytechnic Institute and State University | 2006-2009 | The Development and Implementation Assessment of a Tobacco Use Prevention Model for Youth with Psychiatric Disorders |
| <strong>Donna R. Miles, PhD</strong>&lt;br&gt;Virginia Commonwealth University | 2002-2006 | Genetic and Environmental Factors in the Transition from Tobacco Use to Nicotine Dependence |</p>
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<td>Aashir Nasim, PhD</td>
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<td>Cigarillos, Youth &amp; YouTube: A Content Analysis of Smoking Videograms</td>
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<td>Mary O’Laughlen, PhD</td>
<td>2009-2012</td>
<td>A Decision Aid to Reduce Substance Use Risk Behaviors in Medically At-Risk Adolescents: Targeting Asthma</td>
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<td>Patricia Hollen, PhD</td>
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<td>Susan E. Robinson, PhD</td>
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<td>Sensitivity to Nicotine in Adolescence</td>
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<td>Michael Scott, PhD</td>
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<td>Investigation of Global DNA Methylation following Nicotine Exposure</td>
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<td>Zewelanji Serpell, PhD</td>
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<td>Social Factors Related to Smoking Among Middle and High School Students with ADHD</td>
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<td>James Madison University</td>
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| Zewelanji Serpell, PhD  
Steven W. Evans, PhD  
Virginia State University & James Madison University | 2007-2008 VYTP Small Grants | Preventing Youth Tobacco Use by Treating the Risk-Factor of ADHD: A Follow-up Study of Adolescents with ADHD |
| Robert F. Smith, PhD  
George Mason University | 2002-2006 | A Rodent Model of Adolescent Nicotine Effects |
| Robert F. Smith, PhD  
George Mason University | 2006-2009 | Neurodevelopmental effects of adolescent nicotine |
| Robert F. Smith PhD  
Craig G. McDonald  
George Mason University | 2009-2012 | Adolescent Nicotine: from the First Experience to Neural Remodeling |
| Robert F. Smith PhD  
Craig G. McDonald  
George Mason University | 2012-2015 | Mechanisms of Adolescent Vulnerability to Neurobehavioral Effects of Nicotine |
References
(* indicates VFHY-funded publications)


*Bergstrom, H.C., Smith, R.F., Mollinedo, N.S., McDonald, C.G. (2010). Chronic nicotine exposure produces lateralized, age-dependent dendritic remodeling in the rodent basolateral amygdala. Synapse, 64(10), 754-64.


